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(54) Title: BENZAMIDES AND RELATED INHIBITORS OF FACTOR XA

(57) Abstract: Novel benzamide compounds including their pharmaceutically acceptable isomers, salts,hydrates, solvates and prodrug derivatives having activity against mammalian factor Xa aredescribed. Compositions containing such compounds are also described. The compounds andcompositions are useful *in vitro* or *in vivo* for preventing or treating coagulation disorders.

BENZAMIDES AND RELATED INHIBITORS OF FACTOR Xa

Field of the Invention

This invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa or when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin). In another aspect, the present invention relates to novel monoamidino-containing compounds, their pharmaceutically acceptable salts, and pharmaceutically acceptable compositions thereof which are useful as potent and specific inhibitors of blood coagulation in mammals. In yet another aspect, the invention relates to methods for using these inhibitors as therapeutic agents for disease states in mammals characterized by coagulation disorders.

Background of the Invention

Hemostasis, the control of bleeding, occurs by surgical means, or by the physiological properties of vasoconstriction and coagulation. This invention is particularly concerned with blood coagulation and ways in which it assists in maintaining the integrity of mammalian circulation after injury, inflammation, disease, congenital defect, dysfunction or other disruption. Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

Thrombin is a key enzyme in the coagulation cascade as well as in hemostasis. Thrombin plays a central role in thrombosis through its ability to catalyze the conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson, G., "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. 5, 411-436 (1994). Several classes of anticoagulants currently used in the clinic directly or indirectly affect

thrombin (i.e. heparins, low-molecular weight heparins, heparin-like compounds and coumarins).

A prothrombinase complex, including Factor Xa (a serine protease, the activated form of its Factor X precursor and a member of the calcium ion binding, gamma carboxyglutamyl (Gla)-containing, vitamin K dependent, blood coagulation glycoprotein family), converts the zymogen prothrombin into the active procoagulant thrombin. Unlike thrombin, which acts on a variety of protein substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin. Since one molecule of factor Xa may be able to generate up to 138 molecules of thrombin (Elodi et al., *Thromb. Res.* 15, 617-619 (1979)), direct inhibition of factor Xa as a way of indirectly inhibiting the formation of thrombin may be an efficient anticoagulant strategy. Therefore, it has been suggested that compounds which selectively inhibit factor Xa may be useful as *in vitro* diagnostic agents, or for therapeutic administration in certain thrombotic disorders, see *e.g.*, WO 94/13693.

Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. United States Patent 4,588,587 describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva was shown to be the polypeptide factor Xa inhibitor, antistasin (ATS), by Nutt, E. *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem., 263, 10162-10167 (1988). Another potent and highly specific inhibitor of Factor Xa, called tick anticoagulant peptide (TAP), has been isolated from the whole body extract of the soft tick *Ornithidoros moubata*, as reported by Waxman, L., *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa" Science, 248, 593-596 (1990).

Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, R.R. *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", Thromb. Res., 19, 339-349 (1980); Turner, A.D. *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", Biochemistry, 25,

4929-4935 (1986); Hitomi, Y. *et al.*, "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", Haemostasis, 15, 164-168 (1985); Sturzebecher, J. *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", Thromb. Res., 54, 245-252 (1989); Kam, C.M. *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", Biochemistry, 27, 2547-2557 (1988); Hauptmann, J. *et al.*, *"Comparison* of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", Thromb. Haemost., 63, 220-223 (1990); and the like.

Others have reported Factor Xa inhibitors which are small molecule organic compounds, such as nitrogen containing heterocyclic compounds which have amidino substituent groups, wherein two functional groups of the compounds can bind to Factor Xa at two of its active sites. For example, WO 98/28269 describes pyrazole compounds having a terminal C(=NH)-NH_2 group; WO 97/21437 describes benzimidazole compounds substituted by a basic radical which are connected to a naththyl group via a straight or branched chain alkylene,-C(=O) or -$S(=O)_2$ bridging group; WO 99/10316 describes compounds having a 4-phenyl-N-alkylamidino-piperidine and 4-phenoxy-N-alkylamidino-piperidine group connected to a 3-amidinophenyl group via a carboxamidealkyleneamino bridge; and EP 798295 describes compounds having a 4-phenoxy-N-alkylamidino-piperidine group connected to an amidinonaphthyl group via a substituted or unsubstituted sulfonamide or carboxamide bridging group.

There exists a need for effective therapeutic agents for the regulation of hemostasis, and for the prevention and treatment of thrombus formation and other pathological processes in the vasculature induced by thrombin such as restenosis and inflammation. In particular, there continues to be a need for compounds which selectively inhibit factor Xa or its precursors. Compounds that have different combinations of bridging groups and functional groups than compounds previously discovered are needed, particularly compounds which selectively or preferentially bind to Factor Xa. Compounds with a higher degree of binding to Factor Xa than to

thrombin are desired, especially those compounds having good bioavailability and/or solubility.

Summary of the Invention

As discussed above, a number of non-peptide, specific, factor Xa inhibitors have been described either in the scientific or patent literature (Zhu and Scarborough, Ann. Rep. Med. Chem. 35: 83-102 (2000)). Most of these compounds rely on the interaction of P1 and P4 elements of the inhibitor compounds with the S1 and S4 sub-sites on the factor Xa enzyme. In general, it has been described that P1 elements utilize a highly charged benzamidine functionality in order to interact with the S1 pocket of the factor Xa enzyme. Furthermore, substitution on the benzamidine nitrogens either by alkylation or cyclization (cyclic amidines) of these previously described inhibitors is detrimental to their interaction with the enzyme at the S1 pocket. In the present application, a novel series of inhibitors of factor Xa which do not utilize a S1-interacting benzamidine but utilize a neutral P1 species are described. In addition the compounds also utilize a substituted benzamidine or a cyclic amidine as a P4 element which can each interact with the S4 sub-site of factor Xa enzyme. Surprisingly, the inhibitors of this invention with modified amidine elements are not only of high potency *in vitro*, but also have excellent pharmacological and pharmaceutical properties *in vivo*. These are results that would not have been predicted for such structures.

Accordingly, the present invention relates to novel compounds which inhibit factor Xa, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives, and pharmaceutically acceptable compositions thereof which have particular biological properties and are useful as potent and specific inhibitors of blood coagulation in mammals. In another aspect, the invention relates to methods of using these inhibitors as diagnostic reagents or as therapeutic agents for disease states in mammals characterized by undesired thrombosis or which have coagulation disorders, such as in the treatment or prevention of any thrombotically mediated acute coronary or cerebrovascular syndrome, any thrombotic syndrome occurring in the venous system, any coagulopathy, and any thrombotic complications associated with

extracorporeal circulation or instrumentation, and for the inhibition of coagulation in biological samples.

In certain embodiments, this invention relates to novel compounds which are potent and highly selective inhibitors of isolated factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation cascade (e.g. thrombin, etc.) or the fibrinolytic cascade, and are useful as diagnostic reagents as well as antithrombotic agents.

In one embodiment, the present invention relates to a compound according to the formula (I):

A-Q-D-E-G-J-X (I)

where:

A is selected from:

(a) C_1-C_6-alkyl;

(b) C_3-C_8-cycloalkyl;

(c) -N(R^1,R^2), N(R^1,R^2)-C(=NR^3)-, N(R^1,R^2)-C(=NR^3)-N(R^4)-, R^1-C(=NR^3)-, R^1-C(=NR^3)-N(R^4)-;

(d) phenyl, which is independently substituted with 0-2 R substitutuents;

(e) naphthyl, which is independently substituted with 0-2 R substitutuents; and

(f) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

R is selected from:

H, halo, -CN, -CO_2R^1, -C(=O)-N(R^1, R^2), -$(CH_2)_m$-CO_2R^1, -$(CH_2)_m$-C(=O)-N(R^1, R^2), -NO_2, -$SO_2N(R^1, R^2)$, -SO_2R^1, -$(CH_2)_mNR^1R^2$, -$(CH_2)_m$-C(=NR^3)-R^1, -$(CH_2)_m$-C(=NR^3)-N(R^1,R^2), -$(CH_2)_m$-N(R^4)-C(=NR^3)-N(R^1,R^2), -$(CH_2)_mNR^1$- group appended to a 3 to 6 membered heterocyclic ring containing from 1-4 heteroatoms selected from N, O and S, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CF_3, -OR^2, and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C_1-C_4-alkyl, -C_{1-4}alkyl-CN, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

m is an integer of 0-2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:
H, -OR^5, -N(-R^5, -R^6), -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

R^5 and R^6 are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, -C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

Q is a member selected from the group consisting of:

a direct link, -CH_2-, -C(=O)-, -O-, -N(R^7)-, -N(R^7)CH_2-, - CH_2N(R^7) -, -C(=NR^7)-, -C(=O)-N(R^7)-, -N(R^7)-C(=O)-, -S-, -SO-, -SO_2-, -SO_2-N(R^7)- and –N(R^7)-SO_2-;

R^7 is selected from:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2;

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, -NO_2, -$(CH_2)_nNR^{2a}R^{3a}$, -$(CH_2)_nCO_2R^{2a}$, -$(CH_2)_nCONR^{2a}R^{3a}$, -$SO_2NR^{2a}R^{3a}$, -SO_2R^{2a}, -CF_3, -OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

n is an integer of 0-2;

E is a direct link or a member selected from the group consisting of:

-C_{1-2}-alkyl-, -O-, -S-, -SO-, -SO_2-, -C_{0-1}-alkyl-C(=O), -C_{0-1}-alkyl-C(=O)-N(-R^8)- C_{0-1}-alkyl-, -C_{0-1}-alkyl-N(-R^8)-C(=O)-C_{0-1}-alkyl-, -N(-R^8)-C(=O)-N(-R^8)- and -C_{0-1}-alkyl-N(-R^8)-;

R^8 is a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-C(=O)-OH, -C_{1-4}-alkyl-C(=O)-O-C_{1-4}-alkyl, and -C_{1-4}-alkyl-C(=O)-N(-R^{2b}, -R^{3b});

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

H, -C_{1-4}-alkyl, -C_{0-4}-alkyl-aryl; -C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

Halo; -C_{1-4}-alkyl; -CN, -NO_2; -C(=O)-N(-R^{2c}, -R^{3c}); -C(=O)-OR^{2c}; -$(CH_2)_q$-N(-R^{2c}, -R^{3c}); -SO_2-N(-R^{2c}, -R^{3c}); -SO_2R^{2c}; -CF_3 and -$(CH_2)_q$-OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{1-4}-alkyl-aryl;

q is an integer of 0-2;

G is a member selected from the group consisting of:

(a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein the -C_2-alkenyl or -C_{3-8}-cycloalkenyl are substituted with 0-4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

(c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms

selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

(d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; C_{1-6}-alkyl, carbocylic aryl, -CN; $-NO_2$; $-(CH_2)_{0-6}-NR^{2d}R^{3d}$; $-SO_2NR^{2d}R^{3d}$; $-SO_2R^{2d}$; $-CF_3$; $-(CH_2)_{0-6}-OR^{2d}$; -OH, $-OC_{1-6}$alkyl, ,$-O-(CH_2)_{1-6}OR^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-O-R^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-(CH_2)_{1-6}-N(R^{2d},R^{3d})$; $-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(-(CH_2)_{1-6}-OR^{2d})_2$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-C(=O)-R^{2d}$; $-N(R^{5a})-SO_2-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-O-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-N(R^{2d},R^{3d})$; $-(CH_2)_{0-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; a $-(CH_2)_{0-6}-N(R^{3d})C_{5-6}$ membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a $-(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, -CN; $-NO_2$; carbocylic aryl, -CN; $-NO_2$; or

R^{2d} and R^{3d} taken together with the N atoms they are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

J is a direct link or is a member selected from the group consisting of: $-N(-R^9)-C(=O)-$; $-C(=O)-N(-R^9)-$; $-O-$; $-S-$; $-SO-$; $-SO_2-$; $-CH_2-$; $-N(-R^9)-$; and $-N(-R^9)-SO_2-$;

R^9 is a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl; $-C_{0-4}$-alkyl-carbocyclic aryl; $-(CH_2)_{0-4}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S; $-(CH_2)_{1-6}-C(=O)-O-C_{1-4}$-alkyl; and $-(CH_2)_{1-6}-C(=O)-N(R^{6a},R^{6b})$;

R^{6a} and R^{6b} are each a member independently selected from the group consisting of: H and $-C_{1-6}$-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; -C_{1-4}-alkyl; carbocyclic aryl; -C_{0-2}-alkyl-CN; -O-R^{2e}; -C_{0-2}-alkyl-C(=O)-O-R^{2e}; -C_{0-2}- alkyl-C(=O)-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-NO_2; -C_{0-2}-alkyl-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-SO_2-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-SO_2-R^{2e}; trihaloalkyl; -O-C_{0-2}-alkyl-O-R^{2e}; -C_{0-2}-alkyl-O-R^{2e}; -O-C_{1-4}-alkyl-C(=O)-N(R^{2e}, R^{3e}); -O-C_{1-4}-alkyl-C(=O)-O-R^{2e}; -C_{0-2}-alkyl-N(R^{2e})-C(=O)-R^{3e}; -C_{0-2}-alkyl-N(-R^{2e})-SO_2-R^{3e}; -CH_2-N(R^{2e})-C(=O)-R^{3e} ;-CH_2-N(R^{2e})-SO_2-R^{3e}; -$(CH_2)_{0-6}$-N$R^{2e}R^{3e}$; -C(=O)-N(R^{2e},R^{3e}); -N(-$(CH_2)_{1-6}$-OR^{2e})$_2$; -N(R^{10})-$(CH_2)_{1-6}$-OR^{2e}; -N(R^{10})-C(=O)-R^{2e}; -N(R^{10})-SO_2-R^{2e}; -C(=N(R^{10}))-N(R^{2e},R^{3e}); and a -$(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-2}-alkyl-O-R^{1g}; -C_{0-2}-alkyl-N(-R^{1g}, -R^{2g});-C_{1-4}-alkyl-carbocyclic aryl; -C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are indepedently a member selected from the group of:

H; halo; -C_{1-4}-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -C(=O)-N(R^{3g})R^{4g}; -C(=O)-OR^{3g}; -NO_2; -$(CH_2)_p$-N$R^{3g}R^{4g}$; -SO_2N$R^{3g}R^{4g}$; -SO_2R^{3g}; -CF_3; and -$(CH_2)_p$OR^{3g};

p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In certain aspects of this invention, compounds are provided which are useful as diagnostic reagents. In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. In yet another aspect, the present invention includes methods comprising using the above compounds and pharmaceutical compositions for preventing or treating disease states characterized by undesired thrombosis or disorders of the blood coagulation process in mammals, or for preventing coagulation in stored blood products and samples. Optionally, the methods of this invention comprise administering the pharmaceutical composition in combination with an additional therapeutic agent such as an antithrombotic and/or a thrombolytic agent and/or an anticoagulant.

Detailed Description of the Invention

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkenyl" refers to a trivalent straight chain or branched chain unsaturated aliphatic radical. The term "alkinyl" (or "alkynyl") refers to a straight or branched chain aliphatic radical that includes at least two carbons joined by a triple bond. If no number of carbons is specified alkenyl and alkinyl each refer to radicals having from 2-12 carbon atoms.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain and cyclic groups having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" as used herein refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 14 carbon atoms and preferably 3 to 7 carbon atoms.

As used herein, the terms "carbocyclic ring structure " and " C_{3-16} carbocyclic mono, bicyclic or tricyclic ring structure" or the like are each intended to mean stable ring structures having only carbon atoms as ring atoms wherein the ring structure is a substituted or unsubstituted member selected from the group consisting of: a stable monocyclic ring which is aromatic ring ("aryl") having six ring atoms; a stable monocyclic non-aromatic ring having from 3 to 7 ring atoms in the ring; a stable bicyclic ring structure having a total of from 7 to 12 ring atoms in the two rings wherein the bicyclic ring structure is selected from the group consisting of ring structures in which both of the rings are aromatic, ring structures in which one of the rings is aromatic and ring structures in which both of the rings are non-aromatic; and a stable tricyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein the tricyclic ring structure is selected from the group consisting of: ring structures in which three of the rings are aromatic, ring structures in which two of the rings are aromatic and ring structures in which three of the rings are non-aromatic. In each case, the non-aromatic rings when present in the monocyclic, bicyclic or tricyclic ring structure may independently be saturated, partially saturated or fully saturated. Examples of such carbocyclic ring structures include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), 2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin). Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any carbon atom which results in a stable structure. The term "substituted" as used in conjunction with carbocyclic ring structures means that hydrogen atoms attached to the ring carbon atoms of ring structures described herein may be substituted by one or more of the substituents indicated for that structure if such substitution(s) would result in a stable compound.

The term "aryl" which is included with the term "carbocyclic ring structure" refers to an unsubstituted or substituted aromatic ring, substituted with one, two or three substituents selected from loweralkoxy, loweralkyl, loweralkylamino, hydroxy, halogen, cyano, hydroxyl, mercapto, nitro, thioalkoxy, carboxaldehyde, carboxyl,

carboalkoxy and carboxamide, including but not limited to carbocyclic aryl, heterocyclic aryl, and biaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, loweralkylphenyl, napthyl, biphenyl, phenanthrenyl and naphthacenyl.

The term "arylalkyl" which is included with the term "carbocyclic aryl" refers to one, two, or three aryl groups having the number of carbon atoms designated, appended to an alkyl group having the number of carbon atoms designated. Suitable arylalkyl groups include, but are not limited to, benzyl, picolyl, naphthylmethyl, phenethyl, benzyhydryl, trityl, and the like, all of which may be optionally substituted.

As used herein, the term "heterocyclic ring" or "heterocyclic ring system" is intended to mean a substituted or unsubstituted member selected from the group consisting of stable monocyclic ring having from 5-7 members in the ring itself and having from 1 to 4 hetero ring atoms selected from the group consisting of N, O and S; a stable bicyclic ring structure having a total of from 7 to 12 atoms in the two rings wherein at least one of the two rings has from 1 to 4 hetero atoms selected from N, O and S, including bicyclic ring structures wherein any of the described stable monocyclic heterocyclic rings is fused to a hexane or benzene ring; and a stable tricyclic heterocyclic ring structure having a total of from 10 to 16 atoms in the three rings wherein at least one of the three rings has from 1 to 4 hetero atoms selected from the group consisting of N, O and S. Any nitrogen and sulfur atoms present in a heterocyclic ring of such a heterocyclic ring structure may be oxidized. Unless indicated otherwise the terms "heterocyclic ring" or "heterocyclic ring system" include aromatic rings, as well as non-aromatic rings which can be saturated, partially saturated or fully saturated non-aromatic rings. Also, unless indicated otherwise the term "heterocyclic ring system" includes ring structures wherein all of the rings contain at least one hetero atom as well as structures having less than all of the rings in the ring structure containing at least one hetero atom, for example bicyclic ring structures wherein one ring is a benzene ring and one of the rings has one or more hetero atoms are included within the term "heterocyclic ring systems" as well as

bicyclic ring structures wherein each of the two rings has at least one hetero atom. Moreover, the ring structures described herein may be attached to one or more indicated pendant groups via any hetero atom or carbon atom which results in a stable structure. Further, the term "substituted" means that one or more of the hydrogen atoms on the ring carbon atom(s) or nitrogen atom(s) of the each of the rings in the ring structures described herein may be replaced by one or more of the indicated substituents if such replacement(s) would result in a stable compound. Nitrogen atoms in a ring structure may be quaternized, but such compounds are specifically indicated or are included within the term "a pharmaceutically acceptable salt" for a particular compound. When the total number of O and S atoms in a single heterocyclic ring is greater than 1, it is preferred that such atoms not be adjacent to one another. Preferably, there are no more that 1 O or S ring atoms in the same ring of a given heterocyclic ring structure.

Examples of monocylic and bicyclic heterocylic ring systems, in alphabetical order, are acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazalinyl, carbazolyl, 4aH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pryidooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl,

tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl. Preferred heterocyclic ring structures include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1H-indazolyl, oxazolinyl, or isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocylic ring structures.

As used herein the term "aromatic heterocyclic ring system" has essentially the same definition as for the monocyclic and bicyclic ring systems except that at least one ring of the ring system is an aromatic heterocyclic ring or the bicyclic ring has an aromatic or non-aromatic heterocyclic ring fused to an aromatic carbocyclic ring structure.

The terms "halo" or "halogen" as used herein refer to Cl, Br, F or I substituents. The term "haloalkyl", and the like, refer to an aliphatic carbon radicals having at least one hydrogen atom replaced by a Cl, Br, F or I atom, including mixtures of different halo atoms. Trihaloalkyl includes trifluoromethyl and the like as preferred radicals, for example.

The term "methylene" refers to $-CH_2-$.

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to salts retaining the biological effectiveness and properties of the free bases and which are not biologically

or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicyclic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention that are often shown by *in vitro* assays. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it.

In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention.

Preferred Embodiments

The invention provides a compound according to the formula (I):

A-Q-D-E-G-J-X (I)

where:

A is selected from:

(a) C_1-C_6-alkyl;

(b) C_3-C_8-cycloalkyl;

(c) -N(R^1,R^2), N(R^1,R^2)-C(=NR^3)-, N(R^1,R^2)-C(=NR^3)-N(R^4)-, R^1-C(=NR^3)-, R^1-C(=NR^3)-N(R^4)-;

(d) phenyl, which is independently substituted with 0-2 R substitutuents;

(e) naphthyl, which is independently substituted with 0-2 R substitutuents; and

(f) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected

from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

R is selected from:

H, halo, -CN, $-CO_2R^1$, $-C(=O)-N(R^1, R^2)$, $-(CH_2)_m-CO_2R^1$, $-(CH_2)_m-C(=O)-N(R^1, R^2)$, $-NO_2$, $-SO_2N(R^1, R^2)$, $-SO_2R^1$, $-(CH_2)_mNR^1R^2$, $-(CH_2)_m-C(=NR^3)-R^1$, $-(CH_2)_m-C(=NR^3)-N(R^1,R^2)$, $-(CH_2)_m-N(R^4)-C(=NR^3)-N(R^1,R^2)$, $-(CH_2)_mNR^1-$ C_{3-6}heterocyclics, C_{1-4}alkyl, C_{2-6}alkenyl, C_{2-6}alkynyl, C_{3-8}cycloalkyl, C_{0-4}alkylC_{3-8}cycloalkyl, $-CF_3$, $-OR^2$, and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, CN-C_{1-4}alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl and $-NO_2$;

m is an integer of 0-2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

H, $-OR^5$, $-N(-R^5, -R^6)$, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-C_{0-4}$alkylphenyl and $-C_{0-4}$alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN $-C_1$-

$_4$alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

R^5 and R^6 are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

Q is a member selected from the group consisting of:

a direct link, -CH_2-, -C(=O)-, -O-, -N(R^7)-, -N(R^7)CH_2-, - CH_2N(R^7) -, -C(=NR^7)-, -C(=O)-N(R^7)-, -N(R^7)-C(=O)-, -S-, -SO-, -SO_2-, -SO_2-N(R^7)- and –N(R^7)-SO_2-;

R^7 is selected from:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2;

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, -NO_2, -$(CH_2)_nNR^{2a}R^{3a}$, -$(CH_2)_nCO_2R^{2a}$, -$(CH_2)_nCONR^{2a}R^{3a}$, -$SO_2NR^{2a}R^{3a}$, -SO_2R^{2a}, -CF_3, -OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

n is an integer of 0-2;

E is a direct link or a member selected from the group consisting of:

$-C_{1-2}$-alkyl-, -O-, -S-, -SO-, $-SO_2$-, $-C_{0-1}$-alkyl-C(=O)-,

$-C_{0-1}$-alkyl-C(=O)-N($-R^8$)- C_{0-1}-alkyl-, $-C_{0-1}$-alkyl-N($-R^8$)-C(=O)-C_{0-1}-alkyl-,

-N($-R^8$)-C(=O)-N($-R^8$)- and $-C_{0-1}$-alkyl-N($-R^8$)-;

R^8 is a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl; $-C_{0-4}$-alkylaryl; $-C_{0-4}$-alkyl-heteroaryl; $-C_{1-4}$-alkyl-C(=O)-OH,

$-C_{1-4}$-alkyl-C(=O)-O-C_{1-4}-alkyl, and $-C_{1-4}$-alkyl-C(=O)-N($-R^{2b}$, $-R^{3b}$);

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

H, $-C_{1-4}$-alkyl, $-C_{0-4}$-alkyl-aryl; $-C_{0-4}$-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

Halo; $-C_{1-4}$-alkyl; -CN, $-NO_2$; -C(=O)-N($-R^{2c}$, $-R^{3c}$); -C(=O)-OR^{2c};

$-(CH_2)_q$-N($-R^{2c}$, $-R^{3c}$); $-SO_2$-N($-R^{2c}$, $-R^{3c}$); $-SO_2R^{2c}$; $-CF_3$ and $-(CH_2)_q$-OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl and $-C_{1-4}$-alkyl-aryl;

q is an integer of 0-2;

G is a member selected from the group consisting of:

(a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein C_2-alkenyl or C_{3-8}-cycloalkenyl are substituted with 0-4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

(c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

(d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; C_{1-6}-alkyl, carbocylic aryl, -CN; $-NO_2$; $-(CH_2)_{0-6}-NR^{2d}R^{3d}$; $-SO_2NR^{2d}R^{3d}$; $-SO_2R^{2d}$; $-CF_3$; $-(CH_2)_{0-6}-OR^{2d}$; -OH, $-OC_{1-6}$alkyl , $-O-(CH_2)_{1-6}OR^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-O-R^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-(CH_2)_{1-6}-N(R^{2d},R^{3d})$; $-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(-(CH_2)_{1-6}-OR^{2d})_2$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-C(=O)-R^{2d}$; $-N(R^{5a})-SO_2-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-O-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-N(R^{2d},R^{3d})$; $-(CH_2)_{0-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; and $-(CH_2)_{0-6}-N(-R^{3d})-$ group attached directly by its nitrogen atom to a carbon atom of a 5 to 6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a $-(CH_2)_{0-6}-$ group attached to a 5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, -CN; $-NO_2$; carbocylic aryl, -CN; $-NO_2$; or

R^{2d} and R^{3d} taken together with the N atoms ther are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

J is a direct link or is a member selected from the group consisting of:
$-N(-R^9)-C(=O)-$; $-C(=O)-N(-R^9)-$; $-O-$; $-S-$; $-SO-$; $-SO_2-$; $-CH_2-$; $-N(-R^9)-$; and $-N(-R^9)-SO_2-$;

R^9 is a member selected from the group consisting of:
H; $-C_{1-4}$-alkyl; $-C_{0-4}$-alkyl-carbocyclic aryl; $-(CH_2)_{0-4}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S; $-(CH_2)_{1-6}-C(=O)-O-C_{1-4}$-alkyl; and $-(CH_2)_{1-6}-C(=O)-N(R^{6a},R^{6b})$;

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:
H and $-C_{1-6}$-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups;

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; -C_{1-4}-alkyl; carbocyclic aryl; -C_{0-2}-alkyl-CN; -O-R^{2e}; -C_{0-2}-alkyl-C(=O)-O-R^{2e}; -C_{0-2}- alkyl-C(=O)-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-NO_2; -C_{0-2}-alkyl-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-SO_2-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-SO_2-R^{2e}; trihaloalkyl; -O-C_{0-2}-alkyl-O-R^{2e}; -C_{0-2}-alkyl-O-R^{2e}; -O-C_{1-4}-alkyl-C(=O)-N(R^{2e}, R^{3e}); -O-C_{1-4}-alkyl-C(=O)-O-R^{2e}; -C_{0-2}-alkyl-N(R^{2e})-C(=O)-R^{3e}; -C_{0-2}-alkyl-N(-R^{2e})-SO_2-R^{3e}; -CH_2-N(R^{2e})-C(=O)-R^{3e} ;-CH_2-N(R^{2e})-SO_2-R^{3e}; -$(CH_2)_{0-6}$-N$R^{2e}R^{3e}$; -C(=O)-N(R^{2e},R^{3e}); -N(-$(CH_2)_{1-6}$-OR^{2e})$_2$; -N(R^{10})-$(CH_2)_{1-6}$-OR^{2e}; -N(R^{10})-C(=O)-R^{2e}; -N(R^{10})-SO_2-R^{2e}; -C(=N(R^{10}))-N(R^{2e},R^{3e}); and a -$(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-2}-alkyl-O-R^{1g}; -C_{0-2}-alkyl-N(-R^{1g}, -R^{2g});-C_{1-4}-alkyl-carbocyclic aryl; -C_{1-4}-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are indepedently a member selected from the group of:

H; halo; -C_{1-4}-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; -C(=O)-N(R^{3g})R^{4g}; -C(=O)-OR^{3g}; -NO_2; -$(CH_2)_p$-N$R^{3g}R^{4g}$; -SO_2N$R^{3g}R^{4g}$; -SO_2R^{3g}; -CF_3; and -$(CH_2)_p$OR^{3g};

p is an integer of 0-2; and

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and -C_{0-4}-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

A preferred embodiment of formula I are compounds of formula (Ia):

A-Q-D-E-G-J-X (Ia)

where:

A is selected from:

(a) C_1-C_6-alkyl;

(b) C_3-C_8-cycloalkyl;

(c) -$N(R^1,R^2)$, $N(R^1,R^2)$-$C(=NR^3)$-, $N(R^1,R^2)$-$C(=NR^3)$-$N(R^4)$-, R^1-$C(=NR^3)$-, R^1-$C(=NR^3)$-$N(R^4)$-;

(d) phenyl, which is independently substituted with 0-2 R substitutuents;

(e) naphthyl, which is independently substituted with 0-2 R substitutuents; and

(f) monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

R is selected from:

H, halo, -CN, -CO_2R^1, -C(=O)-N(R^1, R^2), -$(CH_2)_m$-CO_2R^1, -$(CH_2)_m$-C(=O)-N(R^1, R^2), -NO_2, -$SO_2N(R^1, R^2)$, -SO_2R^1, -$(CH_2)_mNR^1R^2$, -$(CH_2)_m$-C(=NR^3)-R^1, -$(CH_2)_m$-C(=NR^3)-N(R^1,R^2), -$(CH_2)_m$-N(R^4)-C(=NR^3)-N(R^1,R^2), -$(CH_2)_mNR^1$- group attached to a 3-6 membered heterocylic ring having from 1 to 3 heteroatoms selected from the group consisting of N, O and S, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CF_3, -OR^2, and a 5-6 membered heterocyclic aromatic or partially saturated system, including imidazoline, containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -methyl, -C_2-C_4-alkyl, -CN, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

m is an integer of 0-2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:

H, -OR^5, -N(-R^5, -R^6), -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

R^5 and R^6 are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, and -NO_2; or

R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

Q is a member selected from the group consisting of:

a direct link, -CH_2-, -C(=O)-, -O-, -NH-, -NMe-, -$NHCH_2$-, -$NMeCH_2$-, -CH_2NH-, -C(=NH)-, -C(=O)-NH-, -NH-C(=O)-, -CH_2NMe-, -C(=NMe)-;

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, -NO_2, -$(CH_2)_nNR^{2a}R^{3a}$, -$(CH_2)_nCO_2R^{2a}$, -$(CH_2)_nCONR^{2a}R^{3a}$, -$SO_2NR^{2a}R^{3a}$, -SO_2R^{2a}, -CF_3, -OR^{2a}, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic system may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylphenyl and -C_{0-4}alkylnaphthyl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

n is an integer of 0-2;

E is a member selected from the group consisting of:

a direct link, -O-, -NH-, -CH_2NH-, -NHCH_2-, -NMe-, -NH-C(=O)-NH-, -C(=O)-NH-, -NH-C(=O)-;

G is a member selected from the group consisting of:

(a) a C_2-alkenyl group or a C_{3-8}-cycloalkenyl group, wherein the alkenyl group and cycloalkenyl group attachment points are the alkenyl carbon atoms and wherein the C_2-alkenyl group or C_{3-8}-cycloalkenyl group is substituted with 0-4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

(c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic- heterocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

(d) an 8-10 membered fused heterocyclic bicyclic ring system, containing 1-4 heteroatoms selected from N, O and S, wherein 0-4 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; C_{1-6}-alkyl, carbocylic aryl, -CN; $-NO_2$; $-(CH_2)_{0-6}-NR^{2d}R^{3d}$; $-SO_2NR^{2d}R^{3d}$; $-SO_2R^{2d}$; $-CF_3$; $-(CH_2)_{0-6}-OR^{2d}$; -OH, $-OC_{1-6}$alkyl , $-O-(CH_2)_{1-6}OR^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-O-R^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-(CH_2)_{1-6}-N(R^{2d},R^{3d})$; $-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(-(CH_2)_{1-6}-OR^{2d})_2$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-C(=O)-R^{2d}$; $-N(R^{5a})-SO_2-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-O-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-N(R^{2d},R^{3d})$; $-(CH_2)_{0-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; and a $-(CH_2)_{0-6}-N(R^{3d})$ group wich is attached via the nitrogen atom to a carbon atom of a 5 to 6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, and a $-(CH_2)_{0-6}-$ group attached to a 5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{5a}, R^{2d}, R^{3d} and R^{4d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, -CN; $-NO_2$; carbocylic aryl, -CN; $-NO_2$; or

R^{2d} and R^{3d} taken together with the N atoms ther are independently attached form a 5-7 membered saturated, partially unsaturated or aromatic heterocyclic ring; or

R^{3d} and R^{4d} taken together with the N atom to which they are attached form a 5-8 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

J is a member selected from the group consisting of:

a direct link, -O-, -NH-, -NMe-, -C(=O)-NH-, -NH-C(=O)-;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) an 8-10 membered fused aromatic heterocyclic bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; -C_{1-4}-alkyl; carbocyclic aryl; -C_{0-2}-alkyl-CN; -O-R^{2e}; -C_{0-2}-alkyl-C(=O)-O-R^{2e}; -C_{0-2}- alkyl-C(=O)-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-NO_2; -C_{0-2}-alkyl-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-SO_2-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-SO_2-R^{2e}; trihaloalkyl; -O-C_{0-2}-alkyl-O-R^{2e}; -C_{0-2}-alkyl-O-R^{2e}; -O-C_{1-4}-alkyl-C(=O)-N(R^{2e}, R^{3e}); -O-C_{1-4}-alkyl-C(=O)-O-R^{2e};

$-C_{0-2}$-alkyl-$N(R^{2e})$-$C(=O)$-R^{3e}; $-C_{0-2}$-alkyl-$N(-R^{2e})$-SO_2-R^{3e}; $-CH_2$-$N(R^{2e})$-$C(=O)$-R^{3e} ;$-CH_2$-$N(R^{2e})$-SO_2-R^{3e}; $-(CH_2)_{0-6}$-$NR^{2e}R^{3e}$; $-C(=O)$-$N(R^{2e},R^{3e})$; $-N(-(CH_2)_{1-6}$-$OR^{2e})_2$; $-N(R^{10})$-$(CH_2)_{1-6}$-OR^{2e}; $-N(R^{10})$-$C(=O)$-R^{2e}; $-N(R^{10})$-SO_2-R^{2e}; $-C(=N(R^{10}))$-$N(R^{2e},R^{3e})$; and a $-(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl; $-C_{0-2}$-alkyl-O-R^{1g}; $-C_{0-2}$-alkyl-$N(-R^{1g}, -R^{2g})$;$-C_{1-4}$-alkyl-carbocyclic aryl; $-C_{1-4}$-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are indepedently a member selected from the group of:

H; halo; $-C_{1-4}$-alkyl, a carbocyclic aryl group; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; $-C(=O)$-$N(R^{3g},R^{4g})$; $-C(=O)$-OR^{3g}; $-NO_2$; $-(CH_2)_p$-$NR^{3g}R^{4g}$; $-SO_2NR^{3g}R^{4g}$; $-SO_2R^{3g}$; $-CF_3$; and $-(CH_2)_pOR^{3g}$;

p is an integer of 0-2; and

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and $-C_{0-4}$-alkyl-carbocyclic aryl;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment of formula I are compounds of formula (Ib):

A-Q-D-E-G-J-X (Ib)

where:

A is selected from:

(a) C_1-C_6-alkyl;

(b) C_3-C_8-cycloalkyl;

(c) -$N(R^1,R^2)$, $N(R^1,R^2)$-$C(=NR^3)$-, $N(R^1,R^2)$-$C(=NR^3)$-$N(R^4)$-, R^1-$C(=NR^3)$-, R^1-$C(=NR^3)$-$N(R^4)$-;

(d) phenyl, which is independently substituted with 0-2 R substitutuents;

(e) naphthyl, which is independently substituted with 0-2 R substitutuents;

(f) a monocyclic or fused bicyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be substituted with 0-2 R substitutuents;

R is selected from:

H, halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, $-CF_3$, -CN, $-(CH_2)_m-CO_2R^1$, $-(CH_2)_m-C(=O)-N(R^1, R^2)$, $-(CH_2)_m-C(=S)-N(R^1, R^2)$, $-NO_2$, $-(CH_2)_m-SO_2N(R^1, R^2)$, $-(CH_2)_m-SO_2R^1$, $-(CH_2)_mNR^1R^2$, $-(CH_2)_mOR^1$, $-(CH_2)_m-C(=NR^3)-R^1$, $-(CH_2)_m-C(=NR^3)-N(R^1,R^2)$, $-(CH_2)_m-N(R^4)-C(=NR^3)-N(R^1,R^2)$, and a 3-8 membered cyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and $-NO_2$;

m is an integer of 0-2;

R^1, R^2, R^3 and R^4 are independently selected from the group consisting of:
H, $-(CH_2)_{0-4}OR^5$, $-(CH_2)_{0-4}-CO_2R^5$, $-(CH_2)_{0-4}N(-R^5, -R^6)$, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-C_{0-4}$alkylaryl and $-C_{0-4}$alkylheteroaryl, and a 3-8 membered cyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl and $-NO_2$; or

R^1 and R^2, or R^2 and R^3 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, where the hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN , $-CO_2R^5$, -OH , $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl and $-NO_2$;

R^5 and R^6 are independently selected from the group consisting of:
H, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, $-C_{0-4}$alkylaryl and $-C_{0-4}$alkylheteroaryl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl, -CN, and $-NO_2$; or

R^5 and R^6 taken together can form a 3-8 membered cycloalkyl or a heterocyclic ring system, wherein the heterocyclic ring system may have from 3 to 10 ring atoms, with 1 to 2 rings being in the ring system and contain from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms

on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, -C_1-C_4-alkyl, -CN -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl and -NO_2;

Q is a member selected from the group consisting of:

a direct link, -CH_2-, -C(=O)-, -O-, -N(R^7)-, -N(R^7)CH_2-, - CH_2N(R^7) -, -C(=NR^7)-, -C(=O)-N(R^7)-, -N(R^7)-C(=O)-, -S-, -SO-, -SO_2-, -SO_2-N(R^7)- and –N(R^7)-SO_2-; preferably, Q is a member selected from the group consisting of: a direct link, -CH_2-, -C(=O)-, -O-, -NH-, -NMe-, -NHCH_2-, -NMeCH_2-, -CH_2NH-, -C(=NH)-, -C(=O)-NH-, -NH-C(=O)-, -CH_2NMe-, -C(=NMe)-;

R^7 is selected from:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-O-C_{1-4}-alkyl, -C_{1-4}-alkyl-N(-C_{1-4}-alkyl, -C_{1-4}-alkyl); -C_{1-4}-alkyl-C(=O)-O-C_{1-4}-alkyl, and -C_{1-4}-alkyl-C(=O)-N(-C_{1-4}-alkyl, -C_{1-4}-alkyl);

D is a direct link or is a member selected from the group consisting of:

(a) phenyl, which is independently substituted with 0-2 R^{1a} substitutuents;

(b) naphthyl, which is independently substituted with 0-2 R^{1a} substitutuents; and

(c) a monocyclic or fused bicyclic heterocyclic ring system having from 5 to 10 ring atoms, wherein 1-4 ring atoms of the ring system are selected from N, O and S, and wherein the ring system may be subsituted from 0-2 R^{1a} substitutuents;

R^{1a} is selected from:

halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN, -NO_2, -$(CH_2)_n$OR^{2a}, -$(CH_2)_n$N$R^{2a}R^{3a}$, -$(CH_2)_n$CO_2R^{2a}, -$(CH_2)_n$CON$R^{2a}R^{3a}$, -SO_2N$R^{2a}R^{3a}$, -SO_2R^{2a}, -CF_3, and a 5-6 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the aromatic heterocyclic

system may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

R^{2a} and R^{3a} are independently selected from the group consisting of:

H, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -C_{0-4}alkylaryl and -C_{0-4}alkylheteroaryl, wherein from 1-4 hydrogen atoms on the ring atoms of the phenyl and naphthyl moieties may be independently replaced with a member selected from the group consisting of halo, -C_{1-4}alkyl, -C_{2-6}alkenyl, -C_{2-6}alkynyl, -C_{3-8}cycloalkyl, -C_{0-4}alkylC_{3-8}cycloalkyl, -CN and -NO_2;

n is an integer of 0-2;

E is a direct link or a member selected from the group consisting of:

-C_{1-2}-alkyl-, -S-, -SO-, -SO_2-, -O-C_{0-1}-alkyl-, -C_{0-1}-alkyl-O-, -C_{0-1}-alkyl-N(-R^8)-, -N(-R^8)-C_{0-1}-alkyl-, -C_{0-1}-alkyl-C(=O)-N(-R^8)-C_{0-1}-alkyl, -C_{0-1}-alkyl-N(-R^8)-C(=O)-C_{0-1}-alkyl-, and - C_{0-1}-alkyl-N(-R^8)-C(=O)-N(-R^8)-C_{0-1}-alkyl-; preferably, E is a member selected from the group consisting of: a direct link, -O-, -NH-, -CH_2NH-, -NHCH_2-, -CH_2O-, -OCH_2-, -NMe-, -NH-C(=O)-NH-, -CH_2-NH-C(=O)-NH-,-C(=O)-NH-, -NH-C(=O)-; -C(=O)-NMe-, -NMe-C(=O)-;

R^8 is a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-OR^{2b}, -C_{1-4}-alkyl-N(-R^{2b}, -R^{3b}); -C_{1-4}-alkyl-C(=O)-OR^{2b}; -C_{1-4}-alkyl-C(=O)-N(-R^{2b}, -R^{3b}); -C_{0-4}-alkyl-C(=O)-R^{2b}; and –C_{0-4}-alkyl-SO_2-R^{2b};

R^{2b} and R^{3b} are each a member independently selected from the group consisting of:

H, -C_{1-4}-alkyl, -C_{1-4}-alkyl-CO_2-C_{0-4}-alkyl, -C_{0-4}-alkyl-aryl; -C_{0-4}-alkyl-heterocyclic group, and R^{2b} and R^{3b} together with the N atom to which

they are attached can form a 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S, wherein the heterocyclic ring may be substituted with 0-2 R^{1c} groups;

R^{1c} is a member selected from the group consisting of:

Halo; -C_{1-4}-alkyl; -CN, -NO_2; -C(=O)-N(-R^{2c}, -R^{3c}); -C(=O)-OR^{2c}; -$(CH_2)_q$-N(-R^{2c}, -R^{3c}); -SO_2-N(-R^{2c}, -R^{3c}); -SO_2R^{2c}; -CF_3 and -$(CH_2)_q$-OR^{2c};

R^{2c} and R^{3c} are each independently a member selected from the group consisting of:

H; -C_{1-4}-alkyl and -C_{1-4}-alkyl-aryl;

q is an integer of 0-2;

G is a member selected from the group consisting of:

(a) C_2-alkenyl or C_{3-8}-cycloalkenyl, wherein the alkenyl and cycloalkenyl attachment points are the alkenyl carbon atoms and wherein the -C_2-alkenyl or -C_{3-8}-cycloalkenyl are substituted with 0-4 R^{1d} groups;

(b) a phenylene group wherein the ring carbon atoms of the phenylene group are substituted with 0-4 R^{1d} groups;

(c) a 3-8 membered a saturated, partially unsaturated or aromatic monocyclic ring system containing 1-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the heterocyclic ring may be substituted with 0-4 R^{1d} groups; and,

(d) an 8-10 membered fused cyclic system, containing 0-4 heteroatoms selected from N, O and S, wherein 0-2 ring atoms of the fused bicyclic ring system may be substituted with 0-4 R^{1d} groups;

R^{1d} is a member selected from the group consisting of:

H, halo; $-CF_3$; $-OCF_3$, $-OCF_2H$, $-OCFH_2$, $-OCH_2CF_3$, $-OCF_2CF_3$, C_{1-6}-alkyl, carbocylic aryl, -CN; $-NO_2$; $-(CH_2)_{0-6}-NR^{2d}R^{3d}$; $-(CH_2)_{0-6}-OR^{2d}$; -OH, $-OC_{1-6}$alkyl, $-O-(CH_2)_{1-6}OR^{2d}$; $-O-(CH_2)_{1-6}-NR^{2d}R^{3d}$; $-N(R^{5a})-(CH_2)_{1-6}-OR^{2d}$; $-N(R^{5a})-(CH_2)_{1-6}-N(R^{2d},R^{3d})$; $-(CH_2)_{0-6}-C(=O)-O-R^{2d}$; $-(CH_2)_{0-6}-C(=O)-N(R^{2d},R^{3d})$; $-O-(CH_2)_{1-6}-C(=O)-O-R^{2d}$; $-O-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(R^{5a})-(CH_2)_{1-6}-C(=O)-O-R^{2d}$; $-N(R^{5a})-(CH_2)_{1-6}-C(=O)-N(R^{2d},R^{3d})$; $-N(-(CH_2)_{1-6}-OR^{2d})_2$; $-N(-(CH_2)_{1-6}-N(R^{2d},R^{3d}))_2$; $-(CH_2)_{0-6}-SO_2NR^{2d}R^{3d}$; $-(CH_2)_{0-6}-SO_2R^{2d}$; $-(CH_2)_{0-6}-N(R^{5a})-C(=O)-R^{2d}$; $-(CH_2)_{0-6}-N(R^{5a})-SO_2-R^{2d}$, $-(CH_2)_{0-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; $-(CH_2)_{0-6}-N(R^{5a})C(=NR^{2d})-R^{4d}$; $-O-(CH_2)_{1-6}-SO_2NR^{2d}R^{3d}$; $-O-(CH_2)_{1-6}-SO_2R^{2d}$; $-O-(CH_2)_{1-6}-N(R^{5a})-C(=O)-R^{2d}$; $-O-(CH_2)_{1-6}-N(R^{5a})-SO_2-R^{2d}$, $-O-(CH_2)_{1-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-O-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; $-O-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-R^{4d}$; $-N(R^{5d})-(CH_2)_{1-6}-SO_2NR^{2d}R^{3d}$; $-N(R^{5d})-(CH_2)_{1-6}-SO_2R^{2d}$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})-C(=O)-R^{2d}$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})-SO_2-R^{2d}$, $-N(R^{5d})-(CH_2)_{1-6}-C(=NR^{2d})-N(R^{3d},R^{4d})$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-N(R^{3d},R^{4d})$; $-N(R^{5d})-(CH_2)_{1-6}-N(R^{5a})C(=NR^{2d})-R^{4d}$; and a 3-8 membered cyclic system containing from 1-4 heteroatoms selected from N, O and S, wherein from 1-4 hydrogen atoms on the heterocyclic ring system may be independently replaced with a member selected from the group consisting of halo, C_1-C_4-alkyl, -CN $-C_{1-4}$alkyl, $-C_{2-6}$alkenyl, $-C_{2-6}$alkynyl, $-C_{3-8}$cycloalkyl, $-C_{0-4}$alkylC_{3-8}cycloalkyl and $-NO_2$;

R^{5a}, R^{2d}, R^{3d}, R^{4d} and R^{5d} are each independently a member selected from the group consisting of:

H, C_{1-6}-alkyl and C_{1-6}-alkylaryl, -CN; $-NO_2$; or

R^{2d} and R^{3d}, or R^{3d} and R^{4d} taken together with the N atoms they are independently attached form a 3-8 membered saturated, partially unsaturated or aromatic heterocyclic ring;

J is a direct link or is a member selected from the group consisting of:

-N(-R^9)-C(=O)-; -C(=O)-N(-R^9)-; -O-; -S-; -SO-; -SO_2-; -SO2N(R9)-, -CH_2-; -N(-R^9)-; and –N(-R^9)-SO_2-; preferably, J is a member selected from the group consisting of: a direct link, -O-, -SO2-, -SO2NH-, -NH-, -NMe-, -C(=O)-NH-, -NH-C(=O)-;

R^9 is a member selected from the group consisting of:

H; -C_{1-4}-alkyl; -C_{0-4}-alkylaryl; -C_{0-4}-alkyl-heteroaryl; -C_{1-4}-alkyl-OR^{6a}, -C_{1-4}-alkyl-N(-R^{6a}, -R^{6b}); -C_{1-4}-alkyl-C(=O)-OR^{6a}, and -C_{1-4}-alkyl-C(=O)-N(-R^{6a}, -R^{6b});

R^{6a} and R^{6b} are each a member independently selected from the group consisting of:

H and -C_{1-6}-alkyl;

X is a member selected from the group consisting of:

(a) phenyl substituted with 0-3 R^{1e} groups;

(b) naphthyl substituted with 0-3 R^{1e} groups and

(c) a 6-membered aromatic heterocyclic ring system containing 1-3 N atoms and having 0-3 ring atoms substituted with 0-3 R^{1e} groups; and

(d) an 8-10 membered fused bicyclic ring system containing 1-4 heteroatoms selected from N, O and S and 0-3 ring atoms of the fused heterocyclic bicyclic ring system are substituted with 0-3 R^{1e} groups;

R^{1e} is a member independently selected from the group consisting of:

Halo; CF_3; -C_{1-4}-alkyl; carbocyclic aryl; -C_{0-2}-alkyl-CN; -O-R^{2e}; -C_{0-2}-alkyl-C(=O)-O-R^{2e}; -C_{0-2}- alkyl-C(=O)-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-NO_2; -C_{0-2}-alkyl-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-SO_2-N(R^{2e}, R^{3e}); -C_{0-2}-alkyl-SO_2-R^{2e}; trihaloalkyl; -O-C_{0-2}-alkyl-O-R^{2e}; -C_{0-2}-alkyl-O-R^{2e}; -O-C_{1-4}-alkyl-

$C(=O)-N(R^{2e}, R^{3e})$; $-O-C_{1-4}$-alkyl-$C(=O)-O-R^{2e}$; $-C_{0-2}$-alkyl-$N(R^{2e})-C(=O)-R^{3e}$; $-C_{0-2}$-alkyl-$N(-R^{2e})-SO_2-R^{3e}$; $-CH_2-N(R^{2e})-C(=O)-R^{3e}$;$-CH_2-N(R^{2e})-SO_2-R^{3e}$; $-(CH_2)_{0-6}-NR^{2e}R^{3e}$; $-C(=O)-N(R^{2e},R^{3e})$; $-N(-(CH_2)_{1-6}-OR^{2e})_2$; $-N(R^{10})-(CH_2)_{1-6}-OR^{2e}$; $-N(R^{10})-C(=O)-R^{2e}$; $-N(R^{10})-SO_2-R^{2e}$; $-C(=N(R^{10}))-N(R^{2e},R^{3e})$; and a $-(CH_2)_{0-6}$-5-6 membered saturated, partially unsaturated or aromatic heterocyclic ring containing 1-4 heteroatoms selected from N, O and S;

R^{10}, R^{2e} and R^{3e} are each independently a member selected from the group consisting of:

H; $-C_{1-4}$-alkyl; $-C_{0-2}$-alkyl-$O-R^{1g}$; $-C_{0-2}$-alkyl-$N(-R^{1g}, -R^{2g})$;$-C_{1-4}$-alkyl-carbocyclic aryl; $-C_{1-4}$-alkyl-heterocyclic; and R^{10} and R^{2e}, or R^{2e} and R^{3e} together with the N atom to which they are attached can form 5-8 membered heterocyclic ring containing 1-4 heteroatoms selected from N, O and S which can be substituted with 0-2 R^{1g} groups;

R^{1g} and R^{2g} are indepedently a member selected from the group of:

H; halo; $-C_{1-4}$-alkyl, a carbocyclic aryl group ; a saturated, partially unsaturated or aromatic heterocyclic group; -CN; $-C(=O)-N(R^{3g})R^{4g}$; $-C(=O)-OR^{3g}$; $-NO_2$; $-(CH_2)_p-NR^{3g}R^{4g}$; $-SO_2NR^{3g}R^{4g}$; $-SO_2R^{3g}$; $-CF_3$; and $-(CH_2)_pOR^{3g}$;

p is an integer of 0-2;

R^{3g} and R^{4g} are each independently selected from the group consisting of:

H; C_{1-4}-alkyl and $-C_{0-4}$-alkyl-carbocyclic aryl;

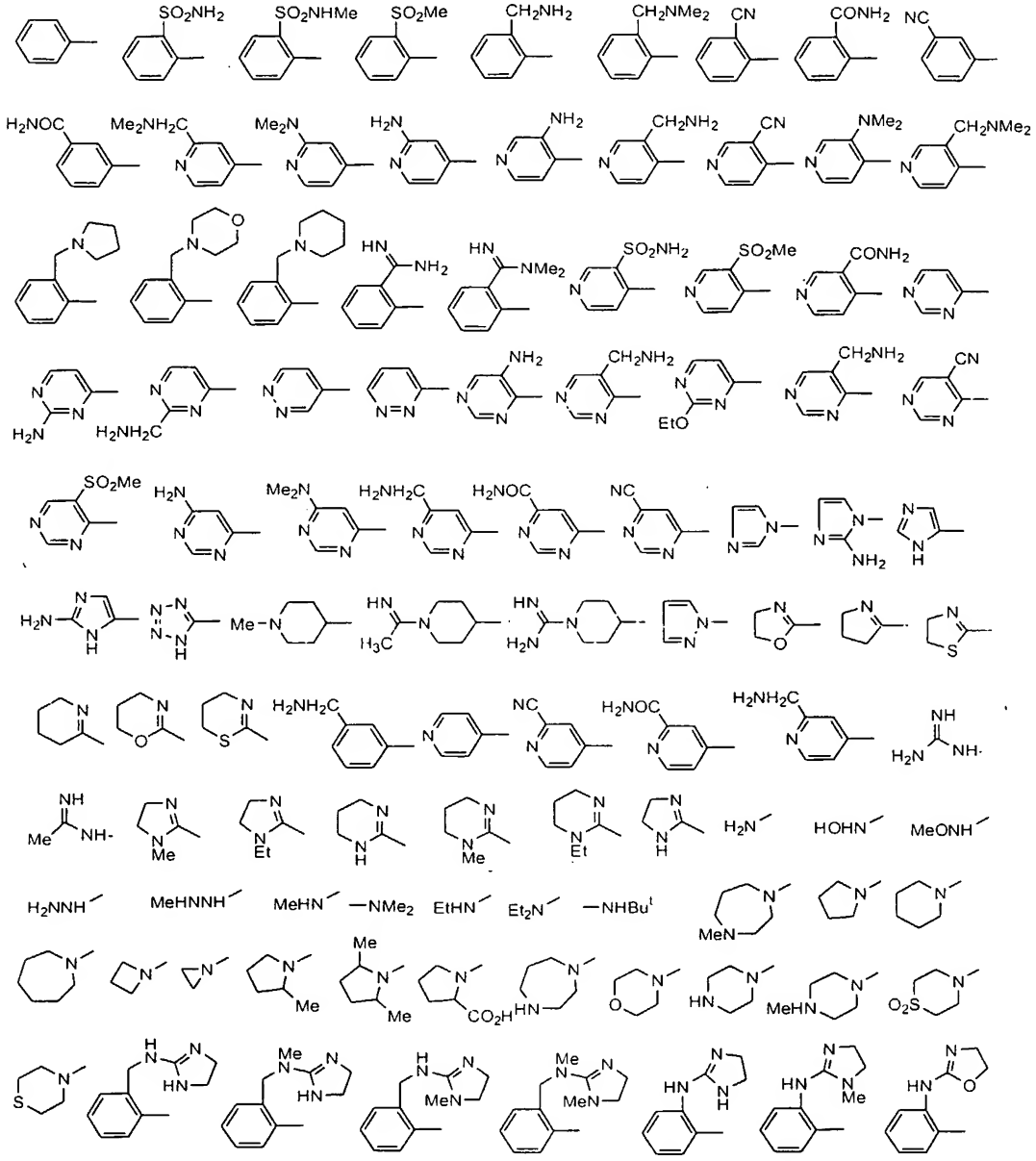
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another preferred embodiment of formula I are compounds of formula (Ic):

A-Q-D-E-G-J-X (Ic)

where:

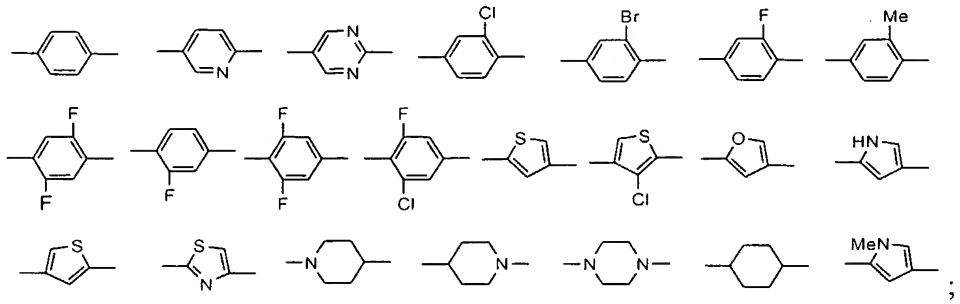
A is a member selected from the group consisting of:



Q is a member selected from the group consisting of:

a direct link, -C(=O)-, -NH-, -NMe-, -NHCH$_2$-, -NMeCH$_2$-, -C(=NH)-, -C(=NMe)-;

D is a direct link or is a member selected from the group consisting of:

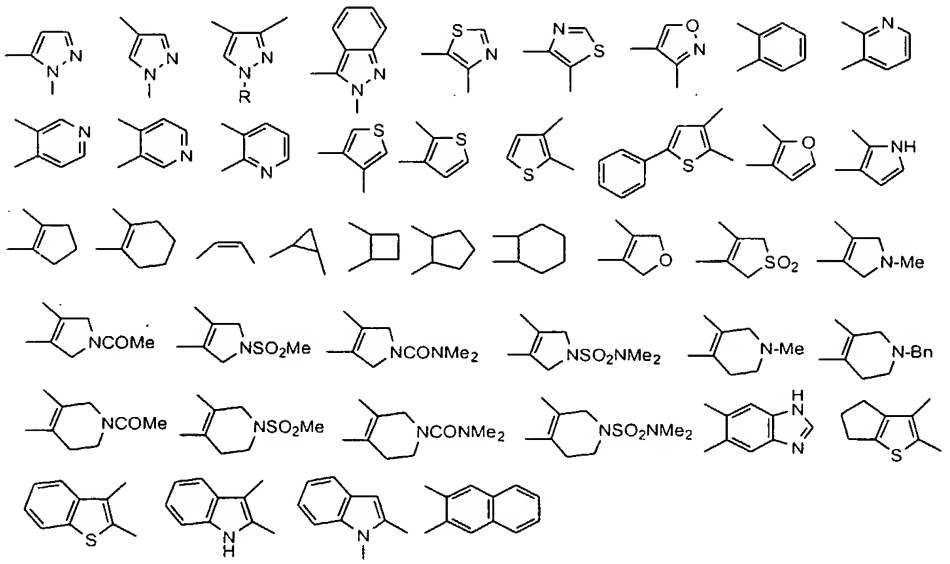


;

E is a member selected from the group consisting of:

a direct link, $-CH_2NH-$, $-C(=O)-NH-$, $-NH-C(=O)-$;

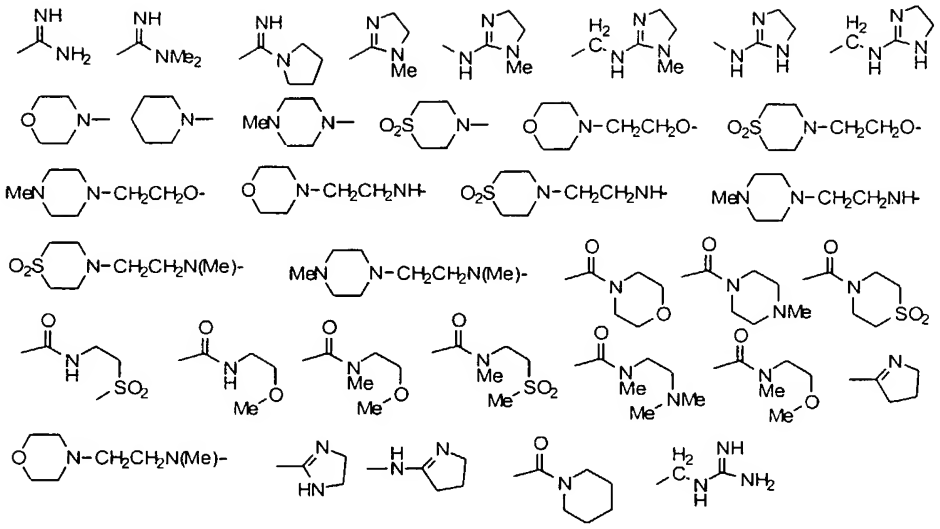
G is a member selected from the group consisting of:



;

G is substituted by 0-4 R^{1d} groups and each R^{1d} group is independently selected from the group consisting of:

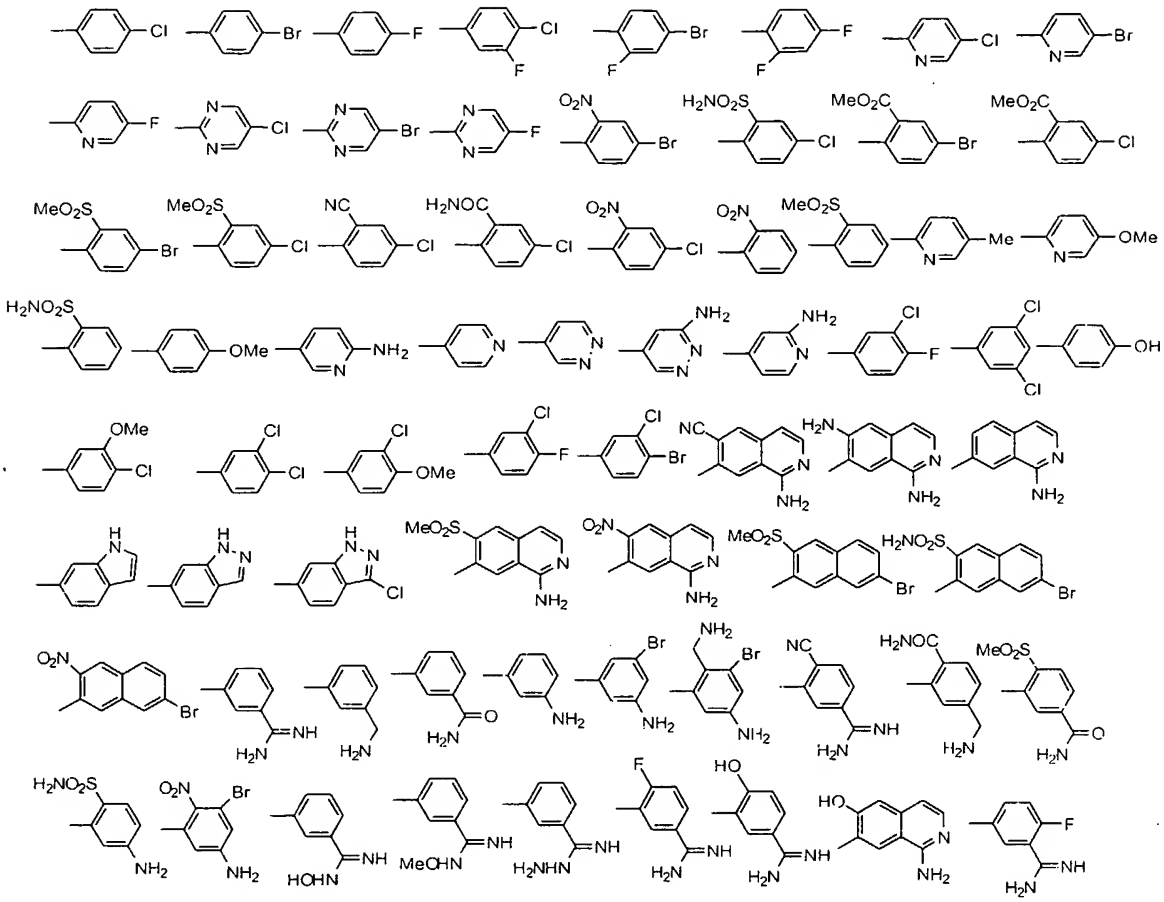
H, $-CH_3$, $-CF_3$, -Cl, -F, -Br, $-NH_2$, $-NMe_2$, -OH, -OMe, $-NHSO_2Me$, $-NO_2$, -CN, $-C(=O)-OMe$, $-CO_2H$, $-CONH_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-NHC(=O)Me$, $-C(=O)N(-Me)_2$, $-CH_2NH_2$, $-CH_2N(-Me)_2$, $-CH_2OH$, $-OCH_2CO_2H$, $-OCH_2C(=O)-OMe$, $-OCH_2C(=O)-NH_2$ and $-OCH_2C(=O)N(-Me)_2$.



J is a member selected from the group consisting of:

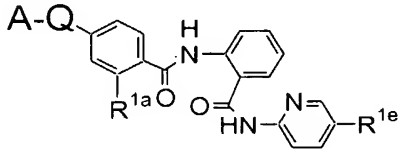
a direct link, -O-, -NH-, -C(=O)-NH- and -NH-C(=O)-;

X is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Still another preferred embodiment of the invention are compounds of the following formula (II):



(II)

where:

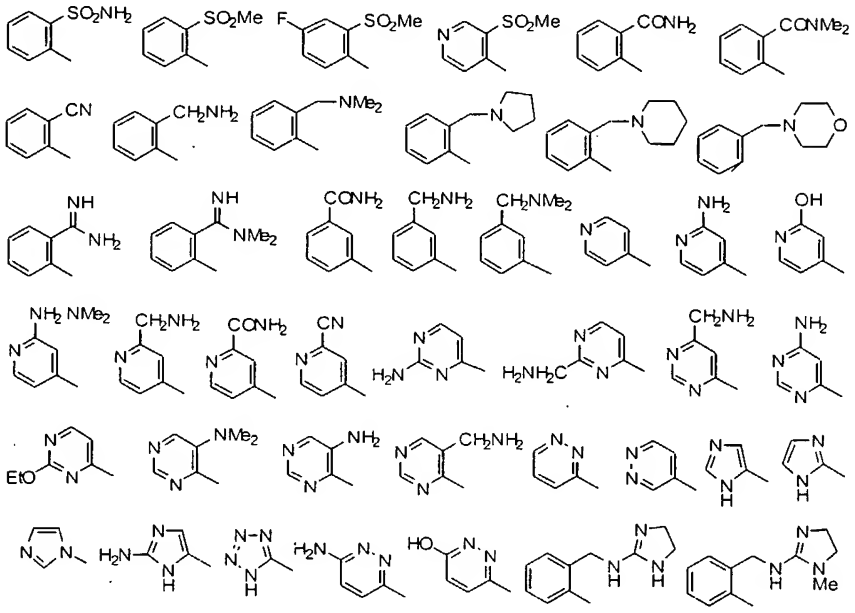
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and –Br;

R^{1e} is a member selected from the group consisting of:

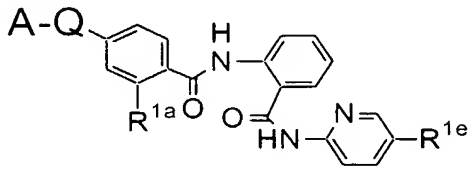
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$; and

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Still another preferred embodiment the invention are compounds of formula (III):



(III)

where:

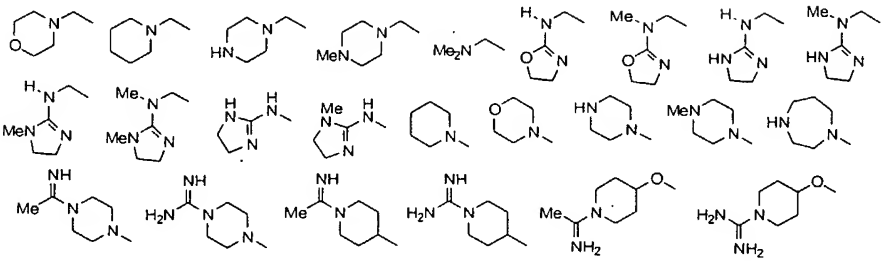
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and –Br;

R^{1e} is a member selected from the group consisting of:

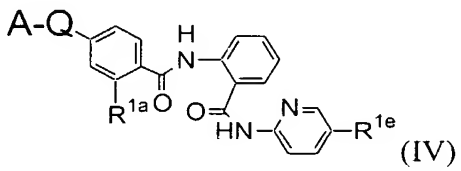
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$; and

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Another further preferred embodiment of the invention are compounds according to the formula (IV):



(IV)

where:

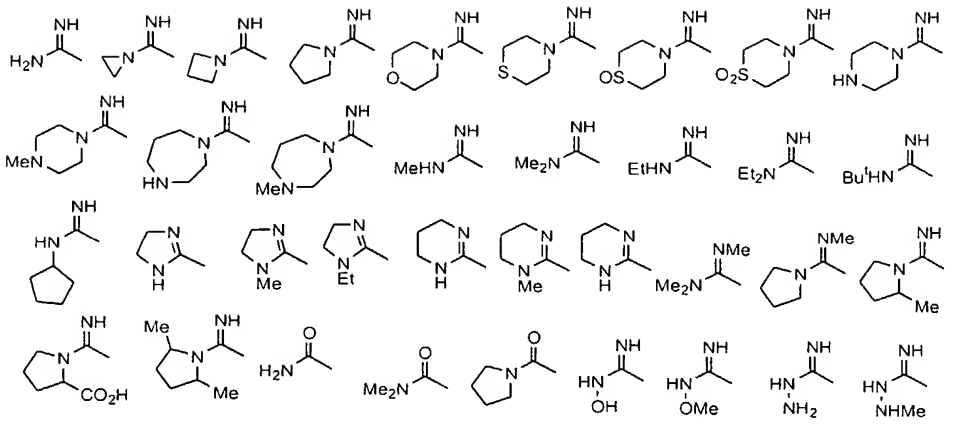
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and –Br;

R^{1e} is a member selected from the group consisting of:

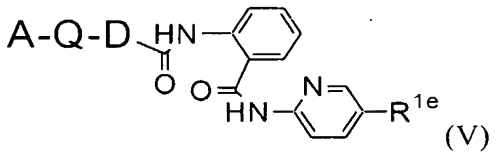
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$;

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

Still another preferred embodiment of the invention are compounds of formula (V):



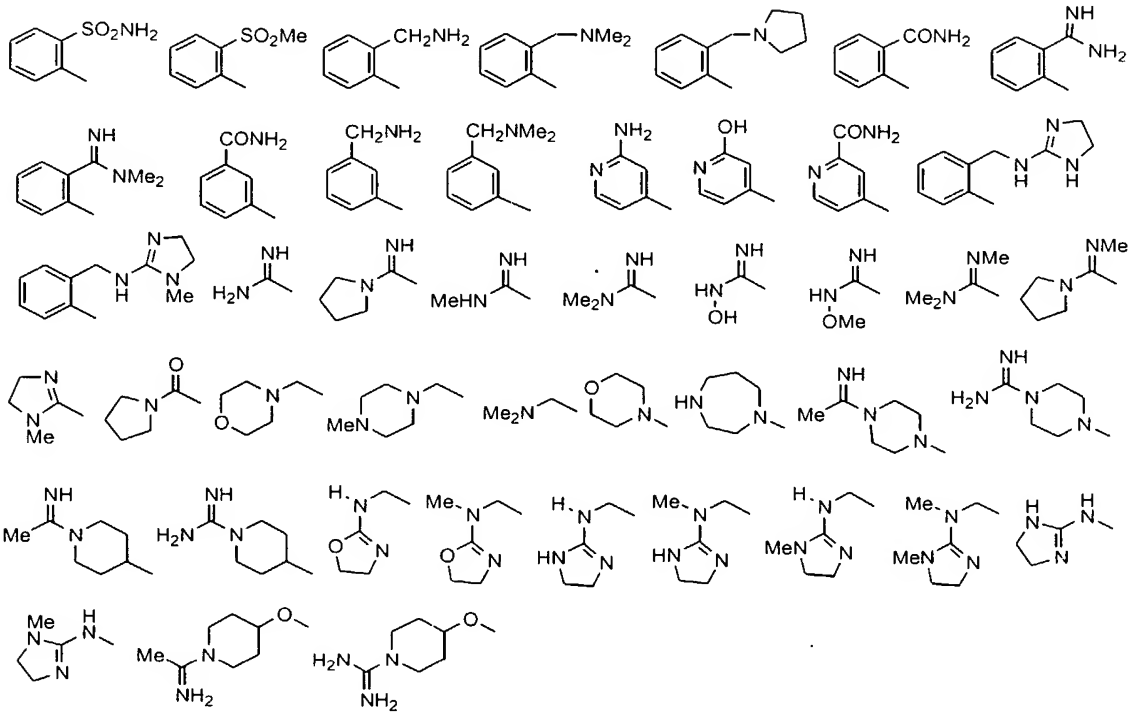
(V)

where:

R^{1e} is a member selected from the group consisting of:

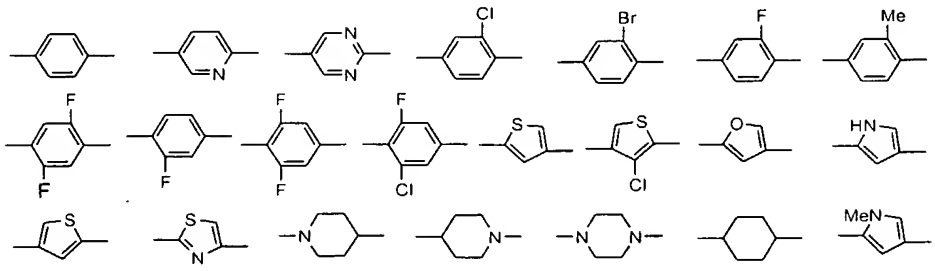
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$;

A-Q is a member selected from the group consisting of:



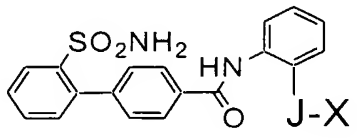
; and

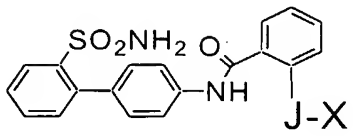
D is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another preferred embodiment, the present invention provides a compound according to the formula:



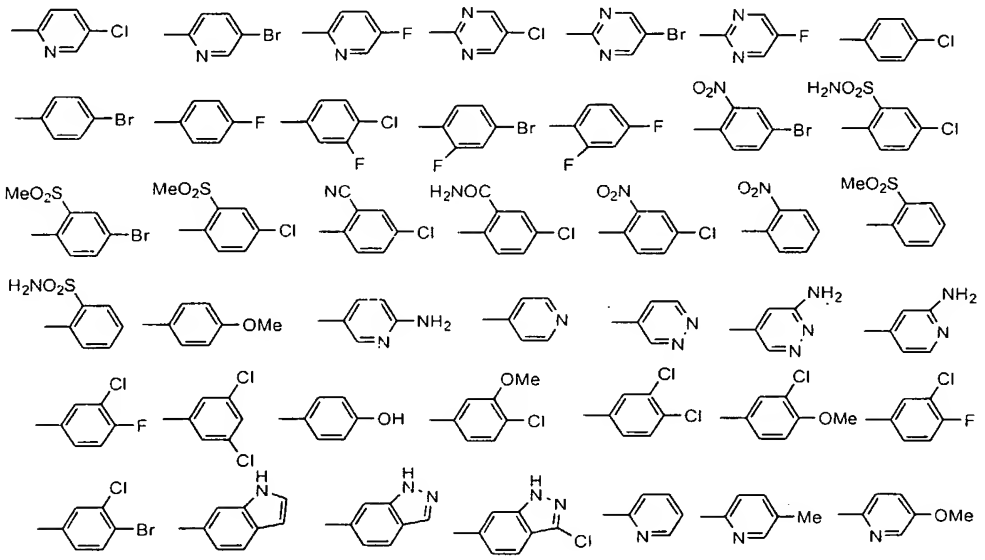


where:

J is a member selected from the group consisting of:

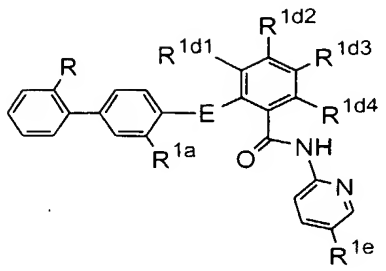
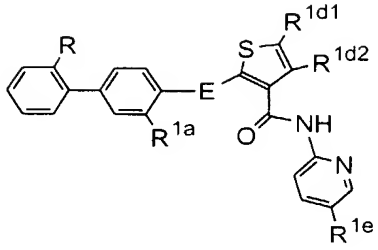
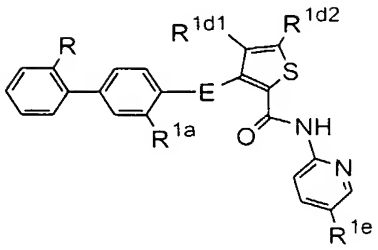
-NHC(=O)-, -C(=O)NH-;

X is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another embodiment the present invention provides a compound according to the formula:

wherein:

R is a member selected from the group of :

$-SO_2-NH_2$ and $-SO_2Me$;

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

E is a member selected from the group consisting of:

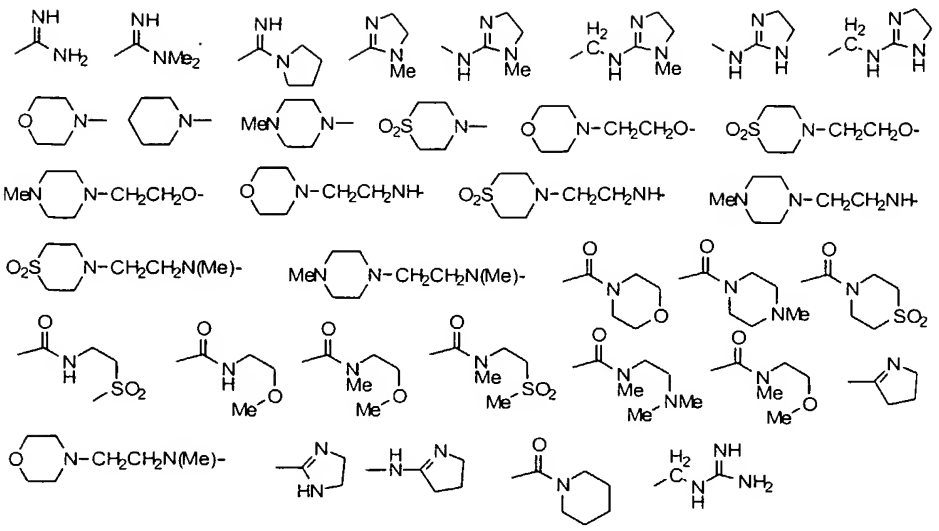
-NHC(=O)- and -C(=O)NH-;

R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

H, -F, -Cl, -Br, -Me, $-NO_2$, -OH, -OMe, $-NH_2$, -NHAc, $-NHSO_2Me$, $-CH_2OH$ and $-CH_2NH_2$;

R^{1d3} is a member selected from the group of:

H, $-CH_3$, $-CF_3$, -Cl, -F, -Br, $-NH_2$, $-N(-Me)_2$, -OH, -OMe, $-NHSO_2Me$, $-NO_2$, -CN, -C(=O)-OMe, $-CO_2H$, -C(=O)-NH_2, $-SO_2NH_2$, $-SO_2CH_3$, -NHC(=O)-Me, -C(=O)-$N(-Me)_2$, $-CH_2NH_2$, $-CH_2-N(-Me)_2$, $-CH_2OH$, $-OCH_2CO_2H$, $-OCH_2C(=O)-OMe$, $-OCH_2C(=O)-NH_2$, and $-OCH_2C(=O)-N(-Me)_2$.

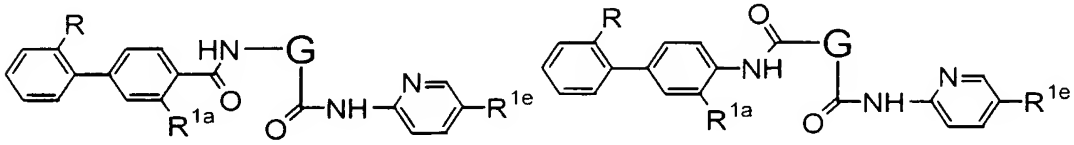


R^{1e} is a member selected from the group of :

F, -Cl, -Br, -OH, -Me and –OMe,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment, the present invention provides a compound according to the formula:



wherein:

R is a member selected from the group consisting of:

$-SO_2NH_2$, $-SO_2Me$;

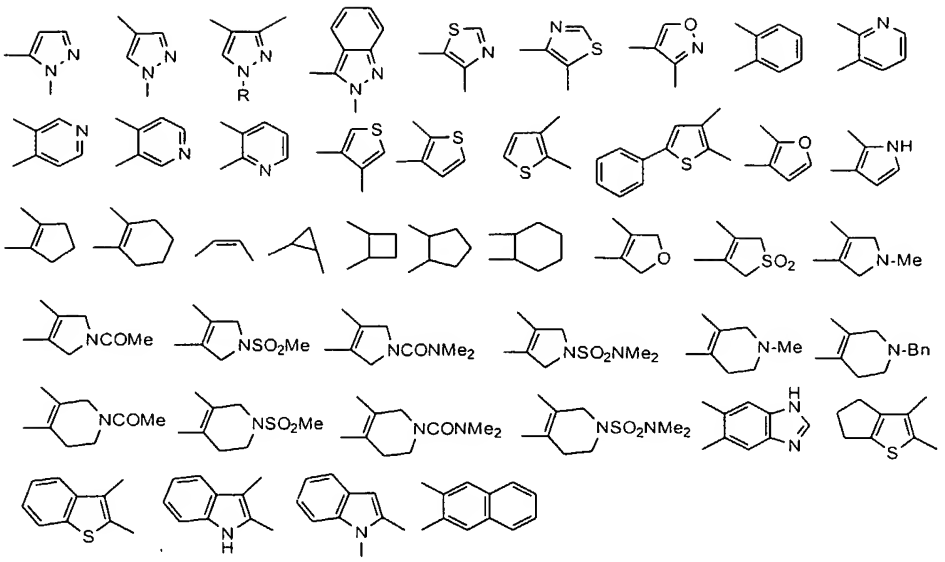
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and Br;

R^{1e} is a member selected from the group consisting of:

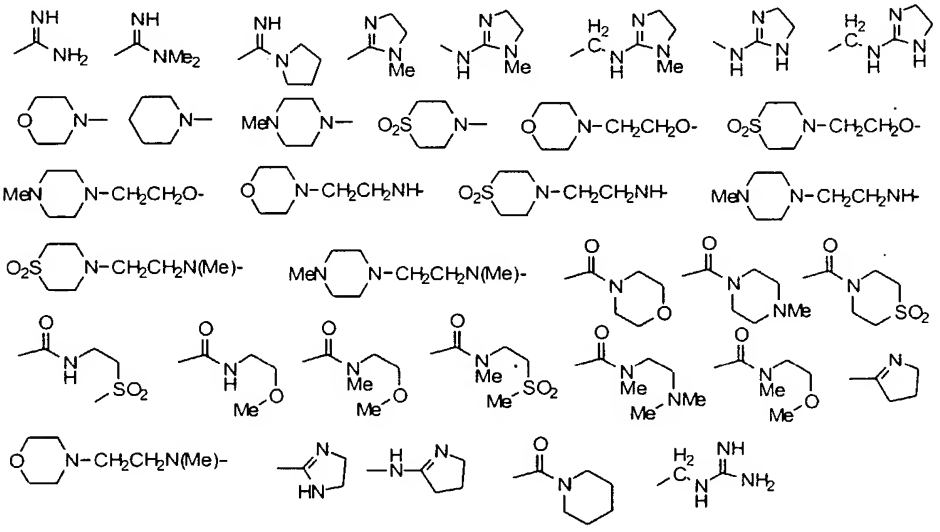
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$; and

G is a member selected from the group consisting of:



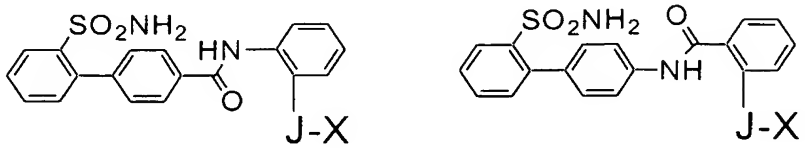
wherein each G group may be substituted by 0-4 R^{1d} groups and each such R^{1d} group is independently selected from the group consisting of:

H, $-CH_3$, $-CF_3$, -Cl, -F, -Br, $-NH_2$, $-N(-Me)_2$, -OH, -OMe, $-NHSO_2Me$, $-NO_2$, -CN, -C(=O)-OMe, $-CO_2H$, $-C(=O)-NH_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-NH-C(=O)-Me$, $-C(=O)-N(-Me)_2$, $-CH_2NH_2$, $-CH_2-N(-Me)_2$, $-CH_2OH$, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-OCH_2C(=O)-NH_2$, $-OCH_2C(=O)-N(-Me)_2$.



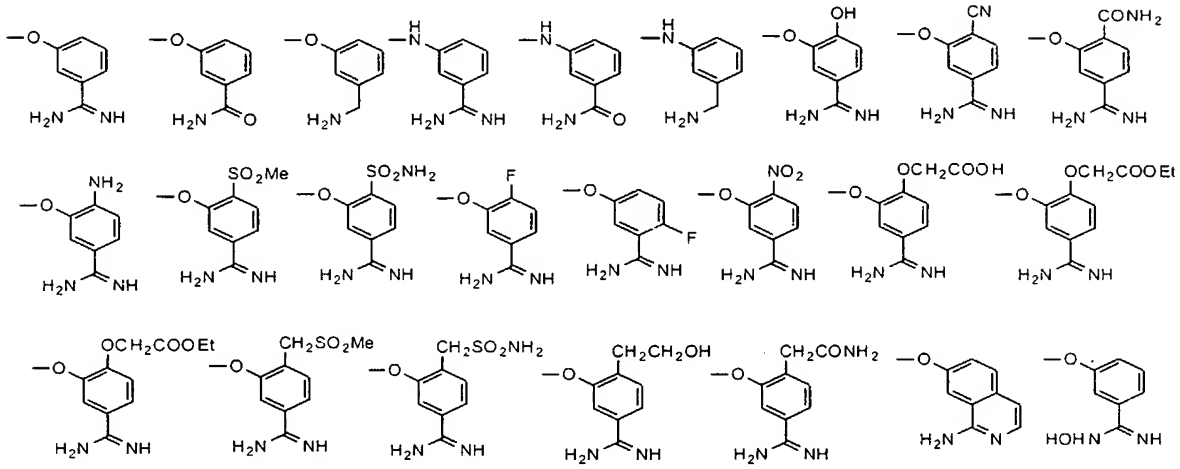
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:



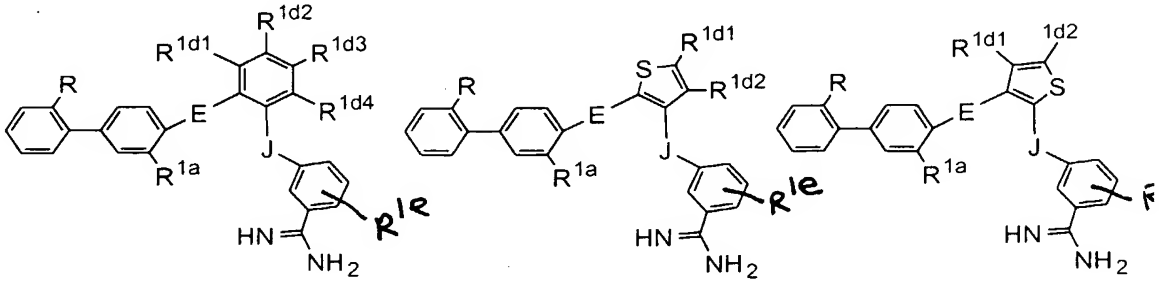
wherein:

J-X are collectively a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another further preferred embodiment the present invention provides a compound according to the formula:



wherein:

R is a member selected from the group of :

$-SO_2NH_2$, and $-SO_2Me$;

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

E is a member selected from the group consisting of:

-NHC(=O)- and -C(=O)NH-;

J is a member selected from the group consisting of:

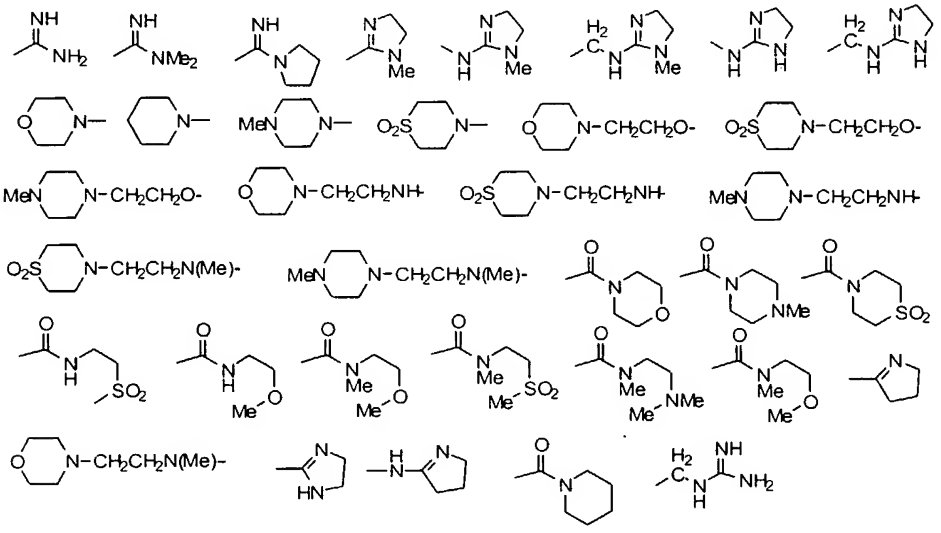
-NHC(=O)- and -C(=O)NH-, O;

R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

H, -F, -Cl, -Br, -Me, $-NO_2$, -OH, -OMe, $-NH_2$, -NHAc, $-NHSO_2Me$, $-CH_2OH$, $-CH_2NH_2$;

R^{1d3} is a member selected from the group of:

H, $-CH_3$, $-CF_3$, -Cl, -F, -Br, $-NH_2$, $-N(-Me)_2$, -OH, -OMe, $-NHSO_2Me$, $-NO_2$, -CN, $-CO_2Me$, $-CO_2H$, $-C(=O)-NH_2$, $-SO_2NH_2$, $-SO_2CH_3$, -NHC(=O)-Me, $-C(=O)-N(-Me)_2$, $-CH_2NH_2$, $-CH_2-N(-Me)_2$, $-CH_2OH$, $-OCH_2CO_2H$, $-OCH_2C(=O)-OMe$, $-OCH_2C(=O)-NH_2$, $-OCH_2C(=O)-N(-Me)_2$.

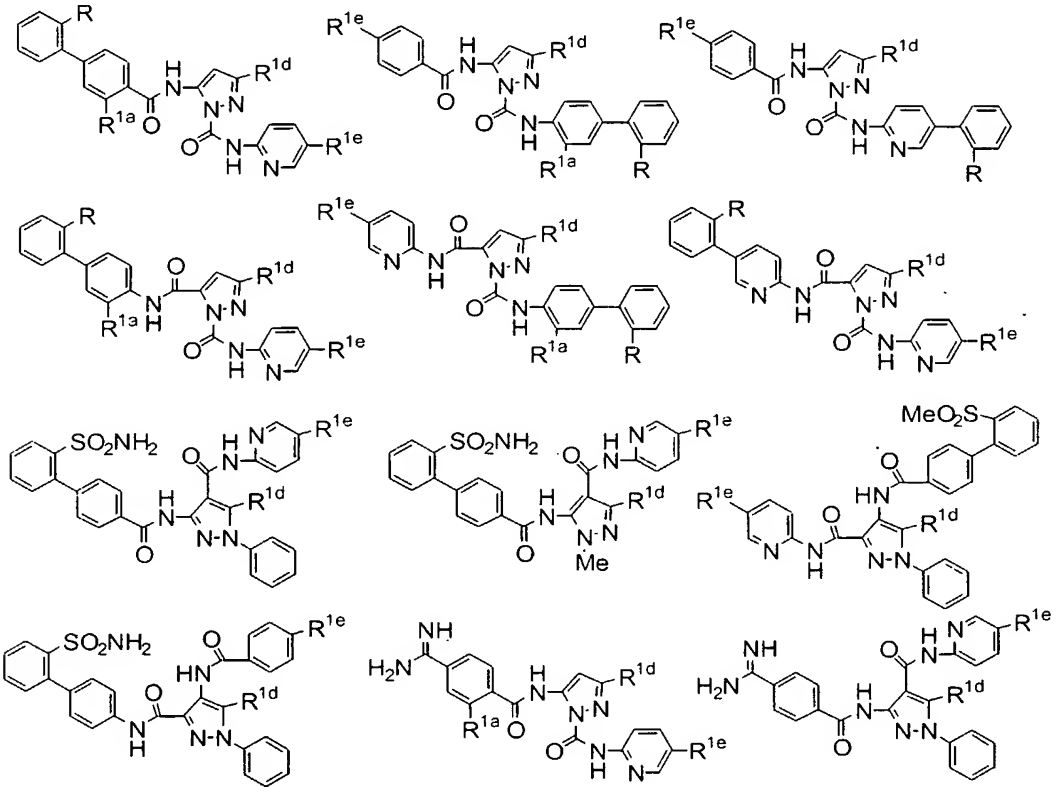


R^{1e} is a member selected from the group of :

F, -Cl, -Br, -OH, -Me and -OMe;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another preferred embodiment, the present invention provides a compound of the following formulae, which illustrate the compounds having preferred substituents for G, particularly when G is a pyrazole ring structure.



wherein:

R is a member selected from the group of :

$-SO_2-NH_2$, and $-SO_2Me$;

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

R^{1d} is a member selected from the group consisting of:

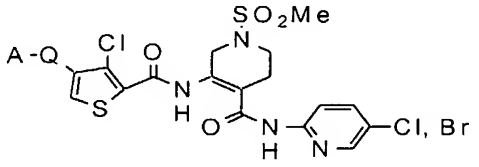
$-H$, $-CH_3$, $-CF_3$, $-CN$, $-SO_2NH_2$ and $-SO_2CH_3$; and

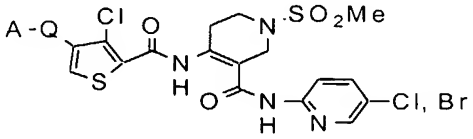
R^{1e} is a member selected from the group of:

-Cl and -Br;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

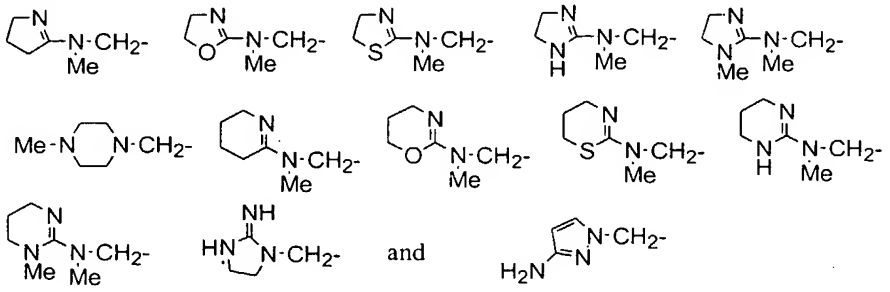
In another preferred embodiment, the present invention provides a compound of the following formulae, which illustrate the compounds having preferred substituents for A-Q taken collectively when the remainder of the compound structure has the one of the following two formulae:





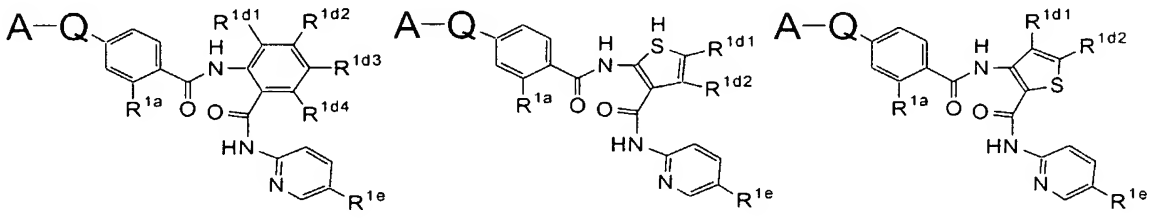
wherein:

A-Q taken together are a member selected from the group consisting of:



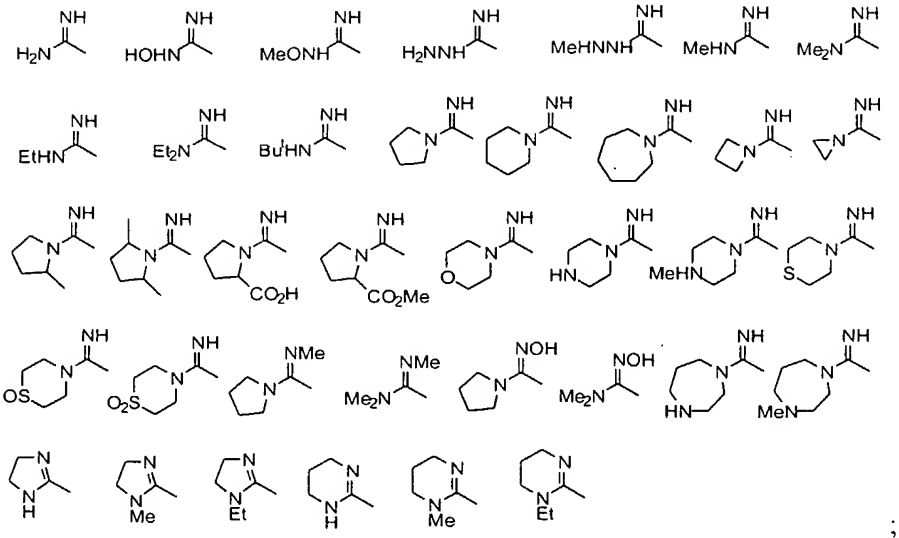
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another preferred embodiment the present invention provides a compound according to the formula:



wherein:

A-Q is a member selected from the group of :



where A-Q may optionally be further substituted with at least one Z' group, where each Z' group is independently a C_1-C_6 alkyl, preferably a C_1-C_3 alkyl group, most preferably a methyl group and where each Z' group may optionally be substituted with a hydroxyl, carboxylic acid or carboxylic acid C_1-C_6 ester group, preferably a hydroxyl, carboxylic acid or carboxylic acid C_1-C_3 ester group, and most preferably, a hydroxyl, carboxylic acid or carboxylic acid methyl ester;

R^{1a} is a member selected from the group of:

H, -F, -Cl and Br;

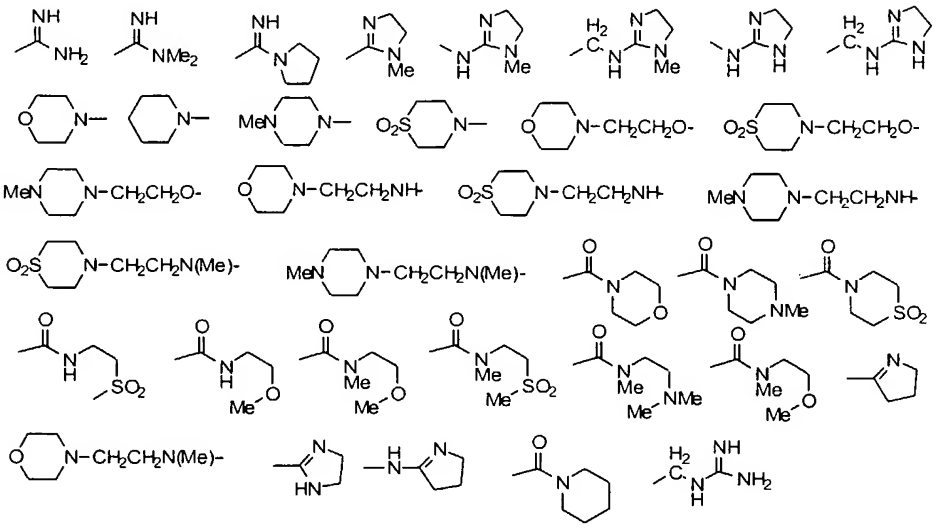
R^{1d1}, R^{1d2}, and R^{1d4} are independently a member selected from the group of:

H, -F, -Cl, -Br, -Me, $-NO_2$, -OH, -OMe, $-NH_2$, -NHAc, $-NHSO_2Me$, $-CH_2OH$, $-CH_2NH_2$

R^{1d3} is a member selected from the group of:

H, $-CH_3$, $-CF_3$, -Cl, -F, -Br, $-NH_2$, $-N(-Me)_2$, -OH, -OMe, $-NHSO_2Me$, $-NO_2$, -CN, -C(=O)-OMe, $-CO_2H$, $-C(=O)-NH_2$, $-SO_2NH_2$, $-SO_2CH_3$, -NHC(=O)-Me,

-C(=O)-N(Me)$_2$, -CH_2NH_2, -CH_2-N(-Me)$_2$, -CH_2OH, -OCH_2CO_2H, -OCH_2C(=O)-OMe, -OCH_2C(=O)-NH_2, -OCH_2C(=O)-N(-Me)$_2$,

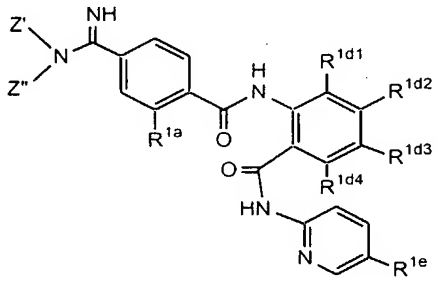


R^{1c} is a member selected from the group of:

F, -Cl, -Br, -OH, -Me and -OMe;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In another embodiment, the invention provides a compound of formula VI:



(VI)

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In formula VI:

Z' and Z" are each independently a C_1-C_6 alkyl, preferably a C_1-C_3 alkyl group, most preferably a methyl group; where Z' and Z" may be optionally substituted with a hydroxyl, carboxylic acid or carboxylic acid C_1-C_6 ester group, preferably a hydroxyl, carboxylic acid or carboxylic acid C_1-C_3 ester group, and most preferably, a hydroxyl, carboxylic acid or carboxylic acid methyl ester;

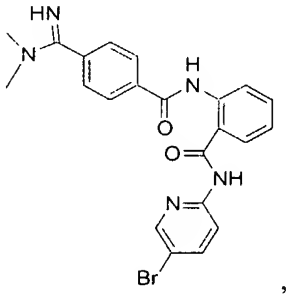
R^{1a} is a member selected from the group of H, -F, -Cl and Br;

R^{1d2} and R^{1d4} are each H;

R^{1d1} and R^{1d3} are each independently a member selected from the group of H, -Cl, -F, -Br, -OH and -OMe; and

R^{1e} is a member selected from the group of -F, -Cl, -Br, -OH, -Me and -OMe.

Examples of suitable compounds of formula VI, as described above, include, but are not limited to:



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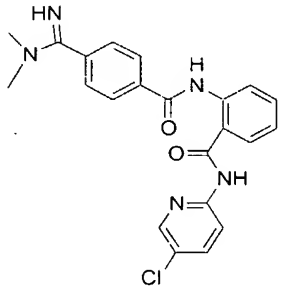

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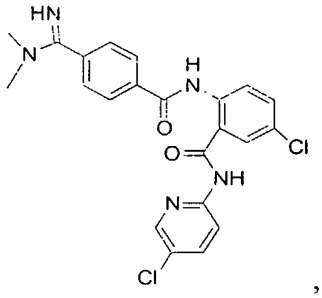

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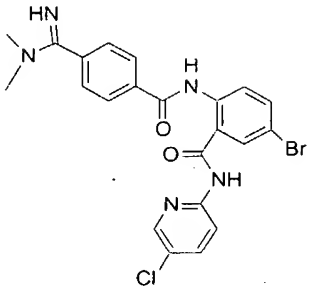
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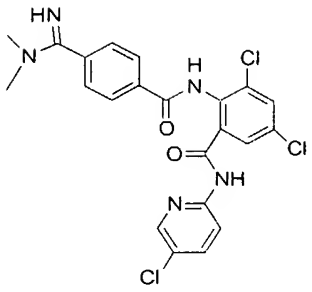
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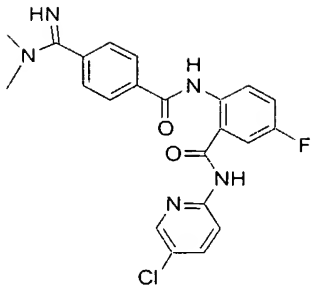
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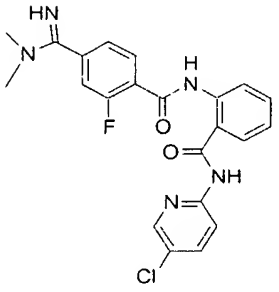
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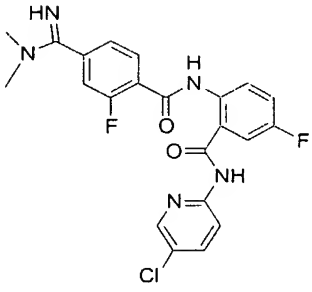
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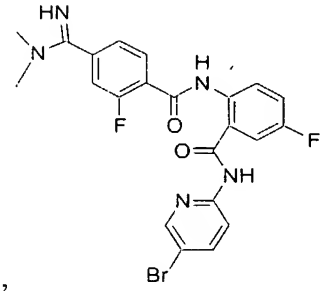
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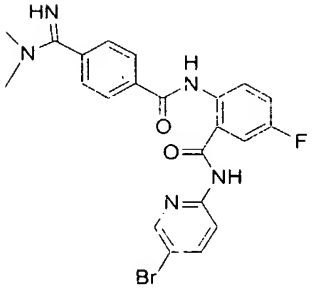
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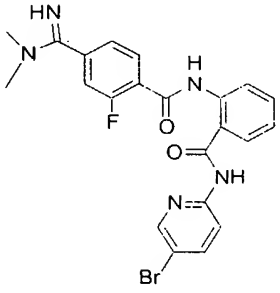
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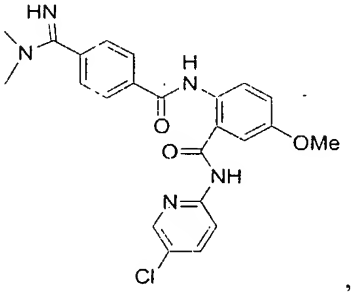
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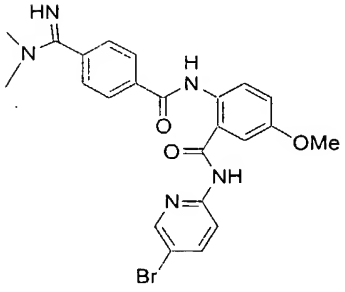
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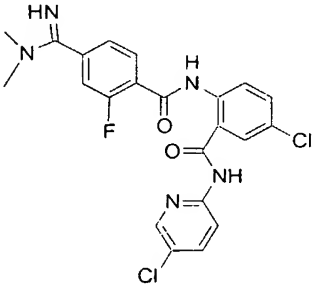
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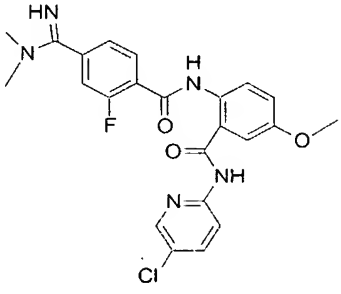
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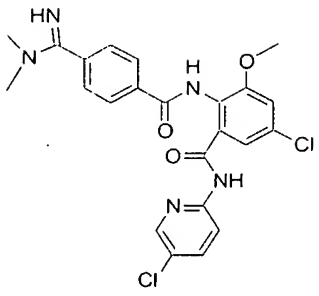
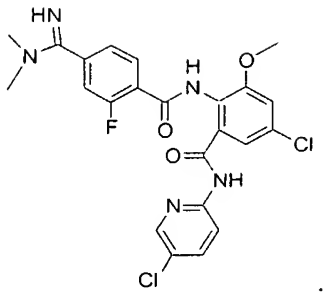
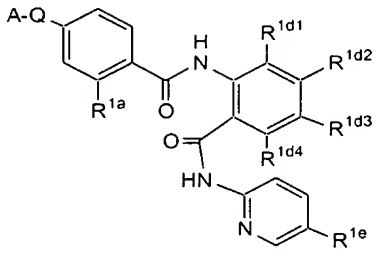


and



In another embodiment, the invention further provides a compound of formula VII:

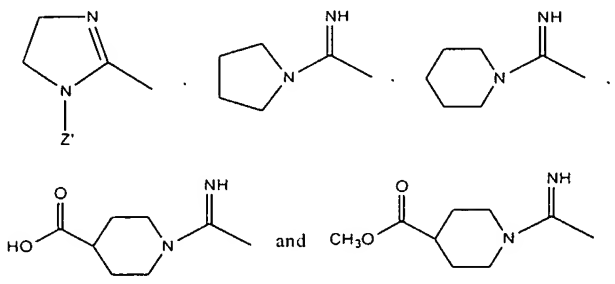


(VII)

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

In formula VII:

A-Q is a member selected from the group of:



where Z' is as described above;

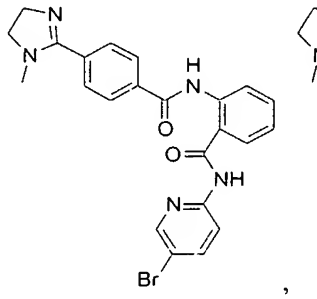
R^{1a} is a member selected from the group of H, -F, -Cl and Br;

R^{1d2} and R^{1d4} are each H;

R^{1d1} is R^{1d3} are each independently a member selected from the group of H, -Cl, -F, -Br, -OH and -OMe;

R^{1e} is a member selected from the group of -F, -Cl, -Br, -OH, -Me and -OMe.

Examples of suitable compounds of formula VII, as described above, include, but are not limited to: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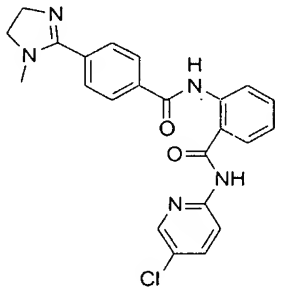
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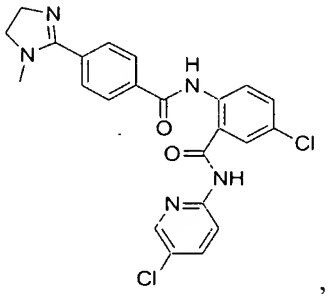
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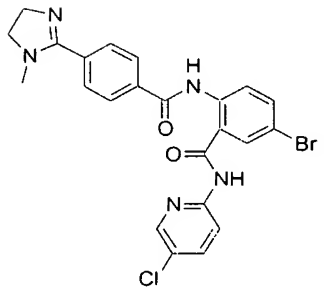
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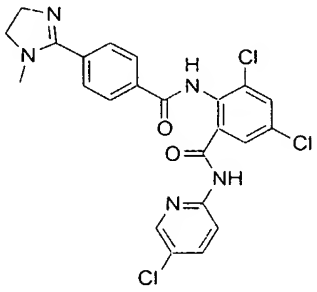
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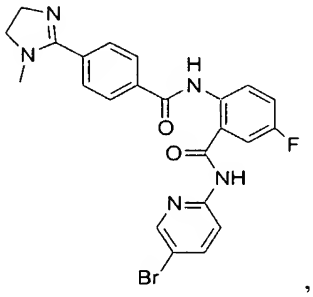
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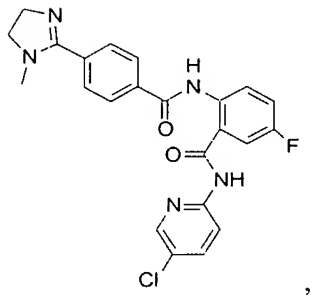
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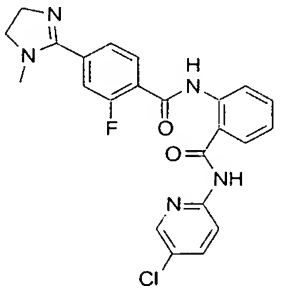
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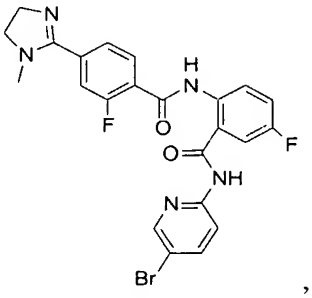
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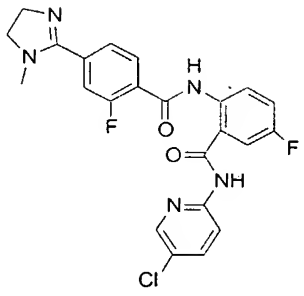
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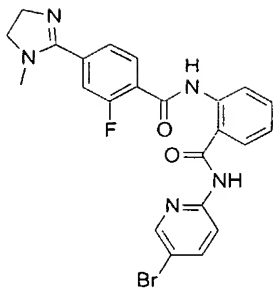
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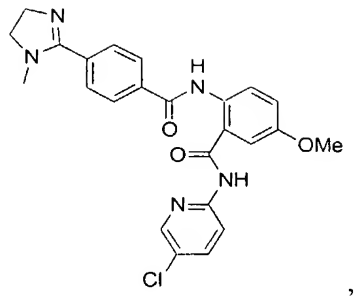
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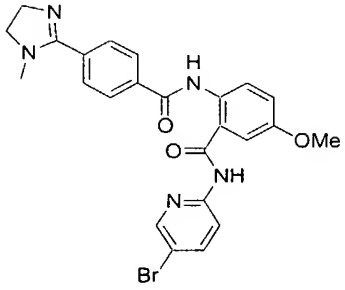
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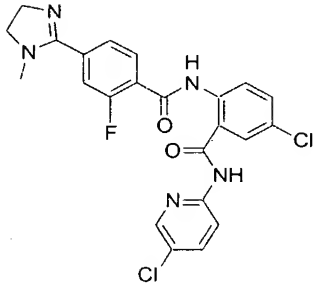
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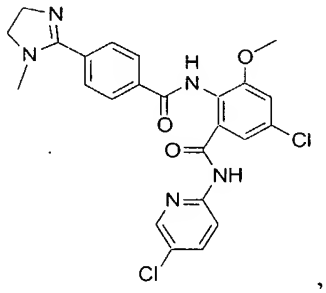
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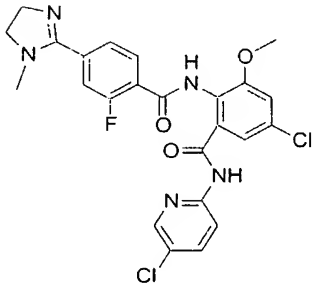
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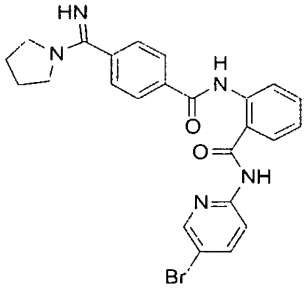
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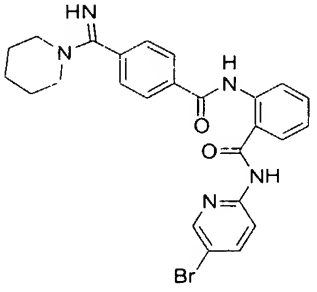
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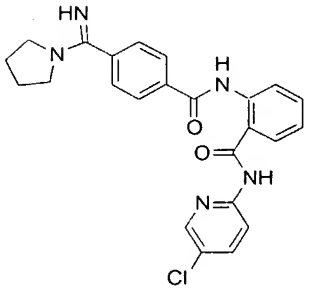
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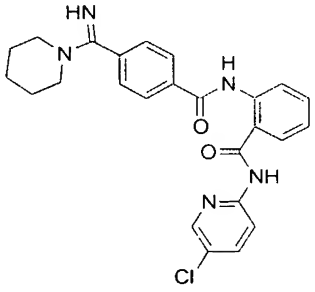
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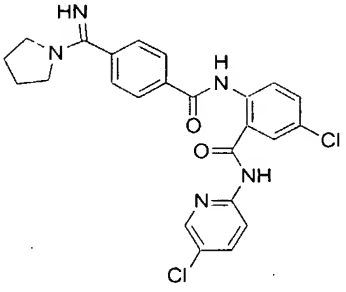
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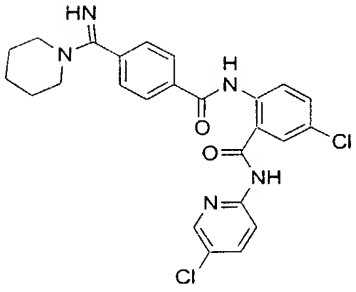
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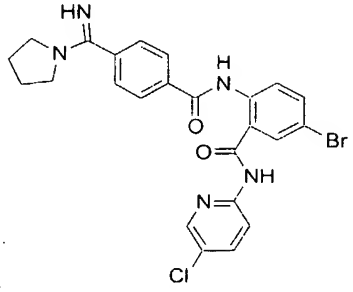
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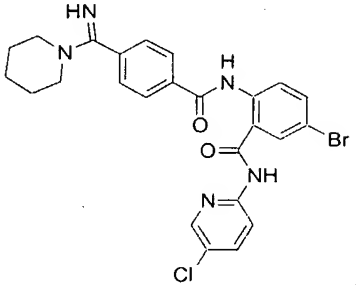
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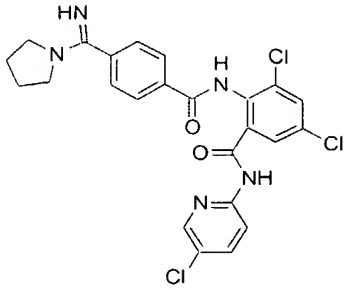
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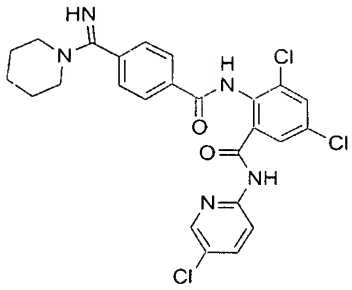
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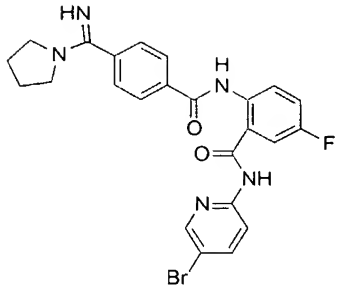
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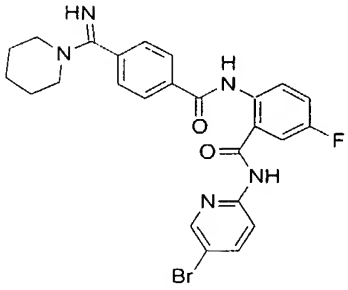
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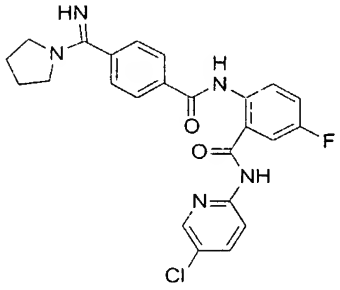
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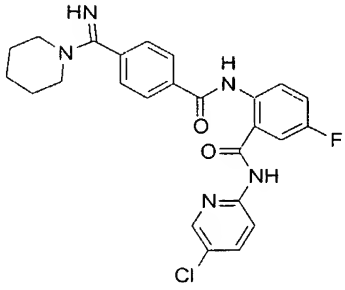
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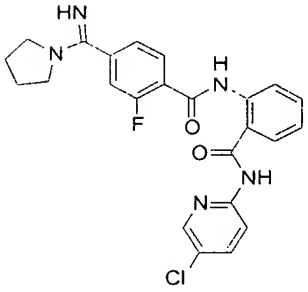
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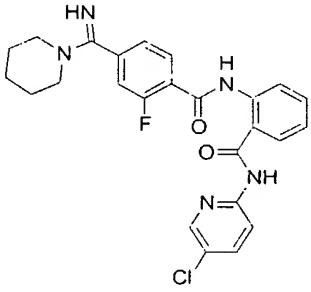
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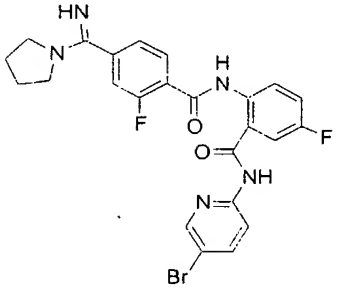
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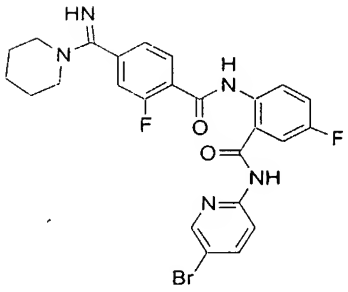
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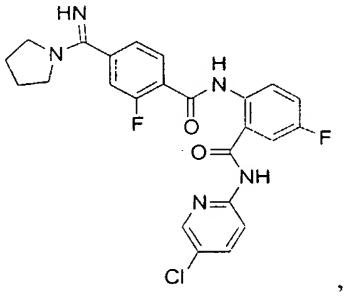
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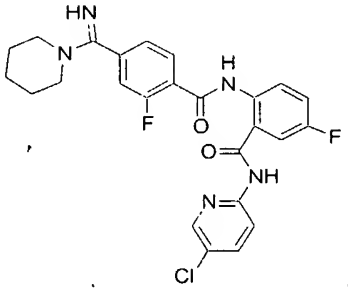
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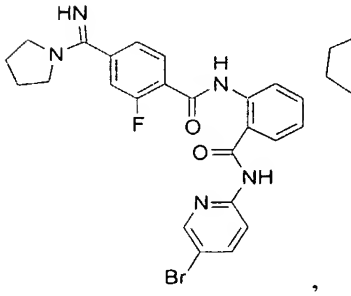
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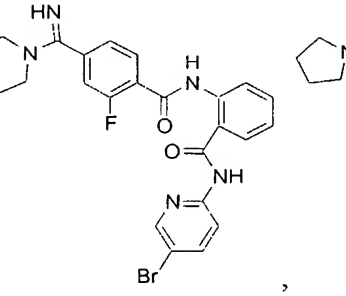
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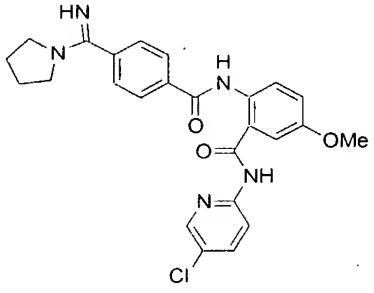
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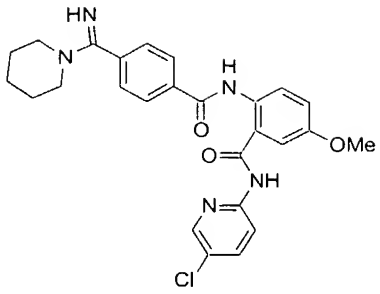

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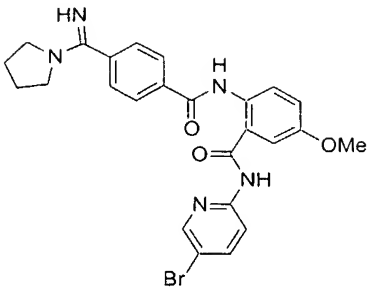

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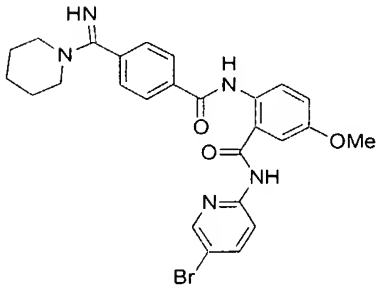

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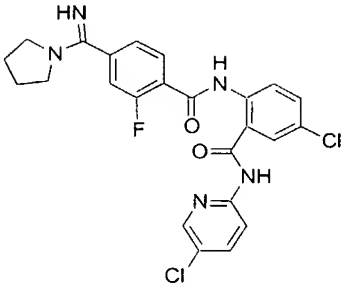

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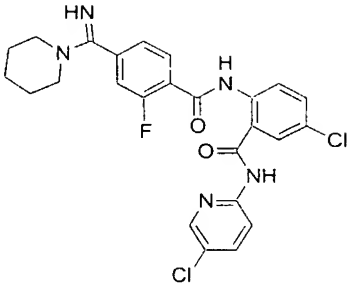
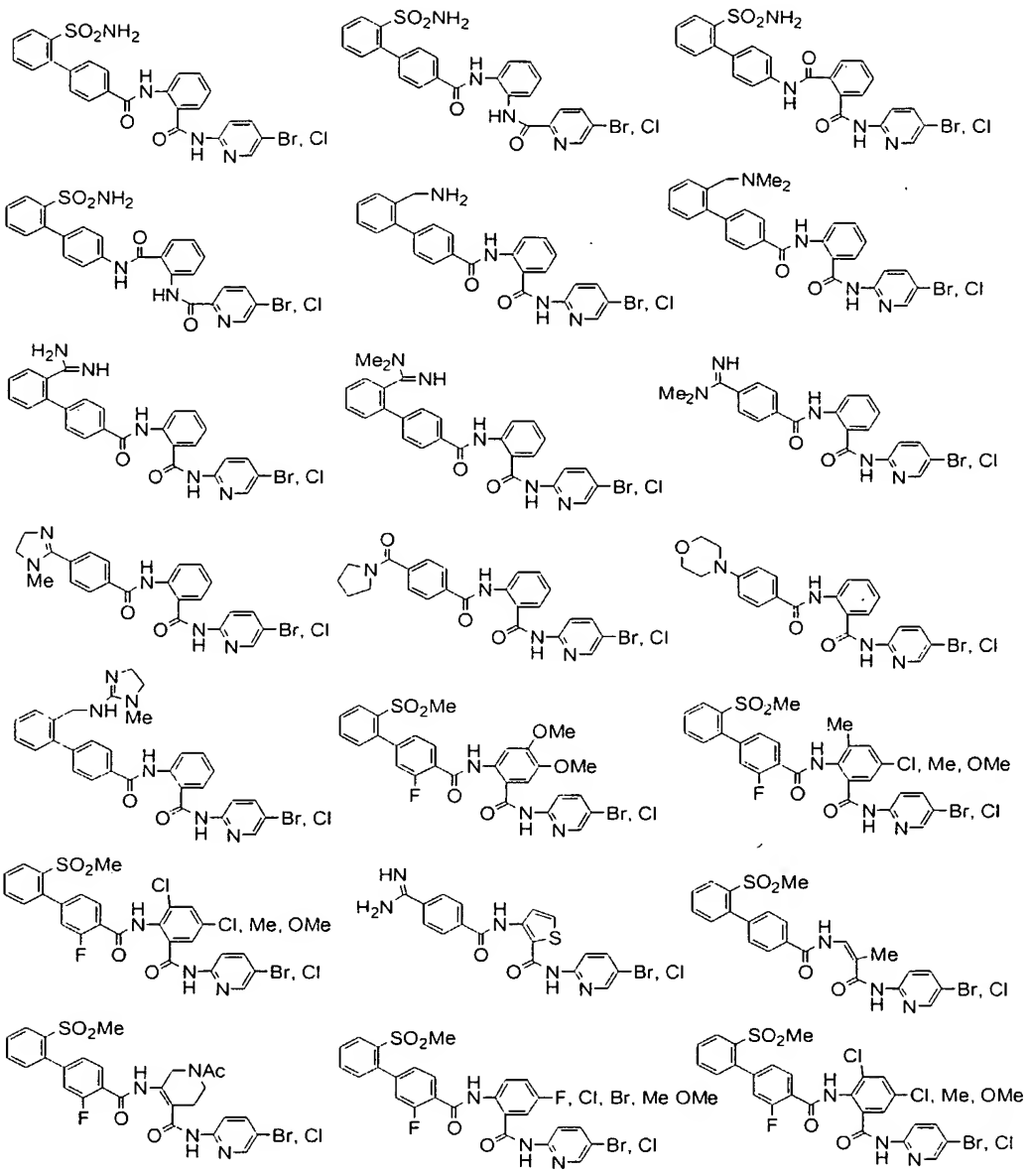


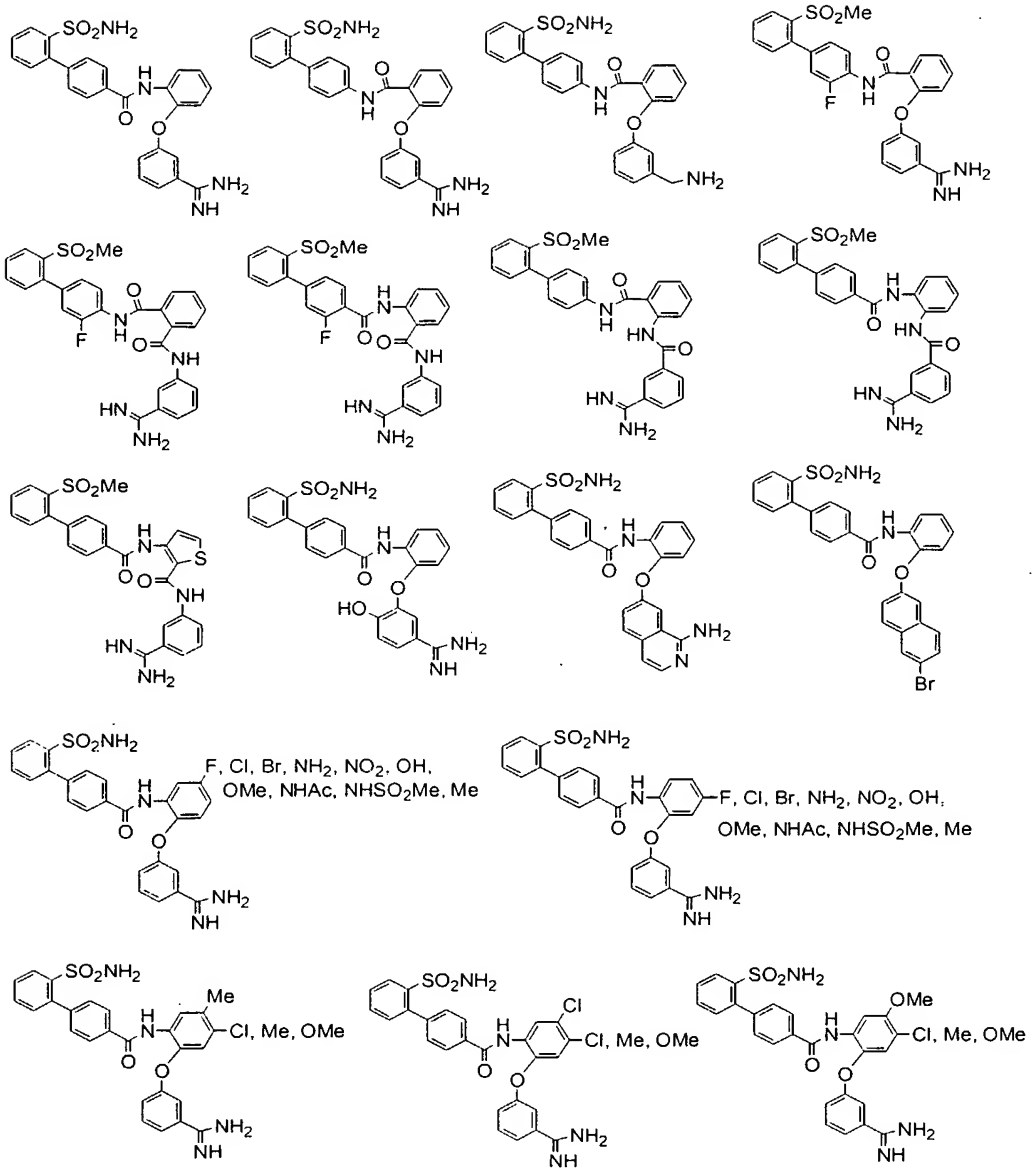
.

In another further preferred embodiment the present invention provides the following compounds:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

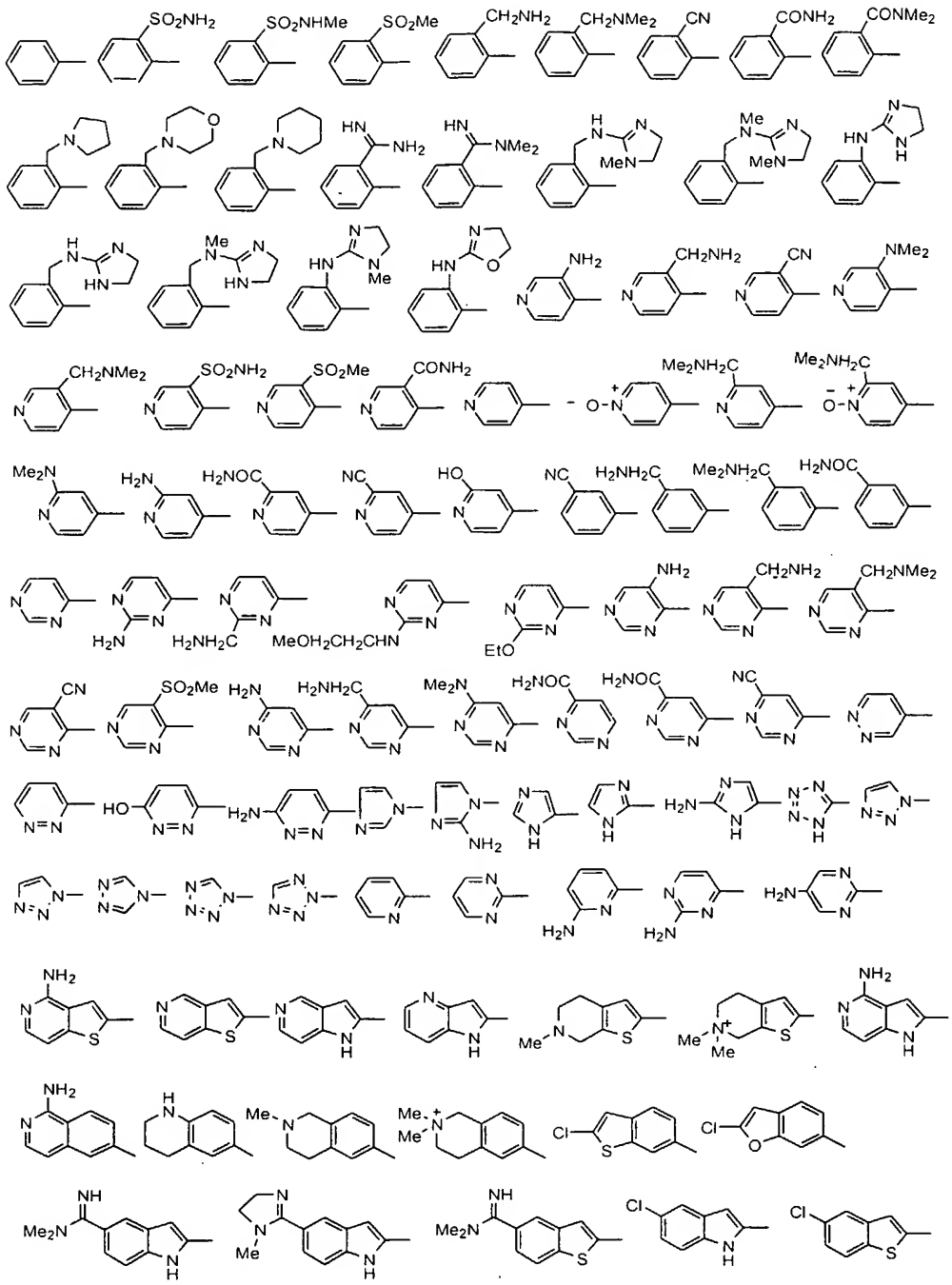
In another further preferred embodiment the present invention provides the following compounds:

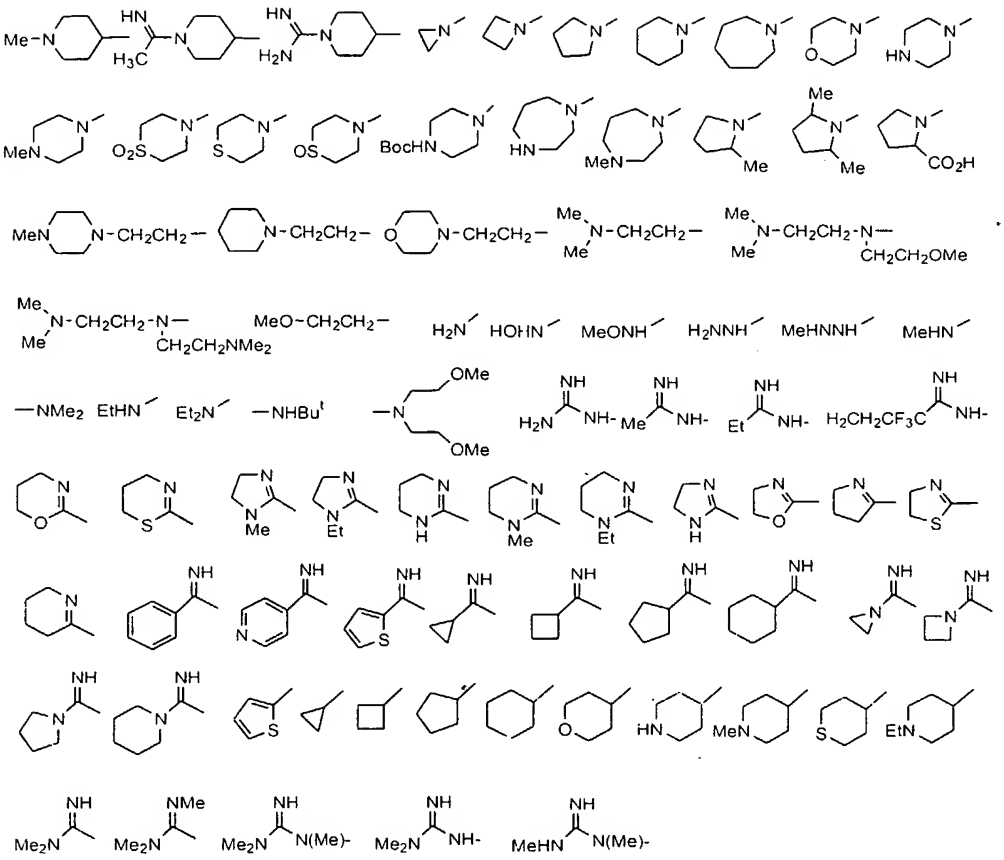


and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention also provides compounds of formula Ib, as set forth above, wherein:

A is a member selected from the group consisting of:

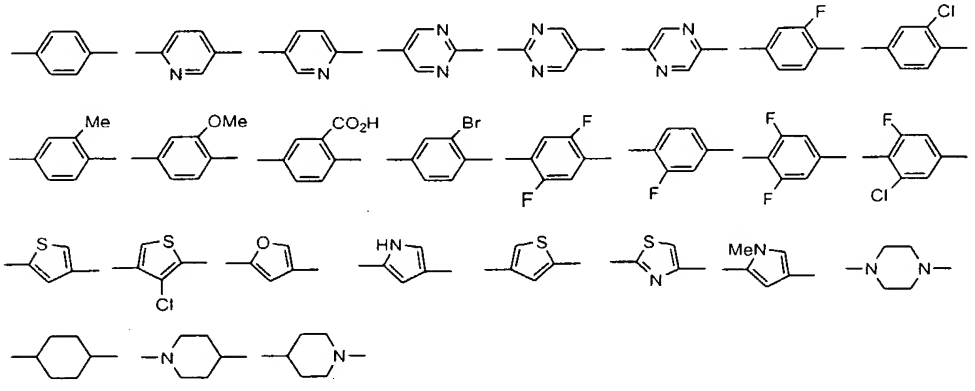




Q is a member selected from the group consisting of:

a direct link, -CH_2-, -C(=O)-, -NH-, -N(Me)-, -$NHCH_2$-, -$N(Me)CH_2$-, -C(=NH)-, -C(=NMe)-;

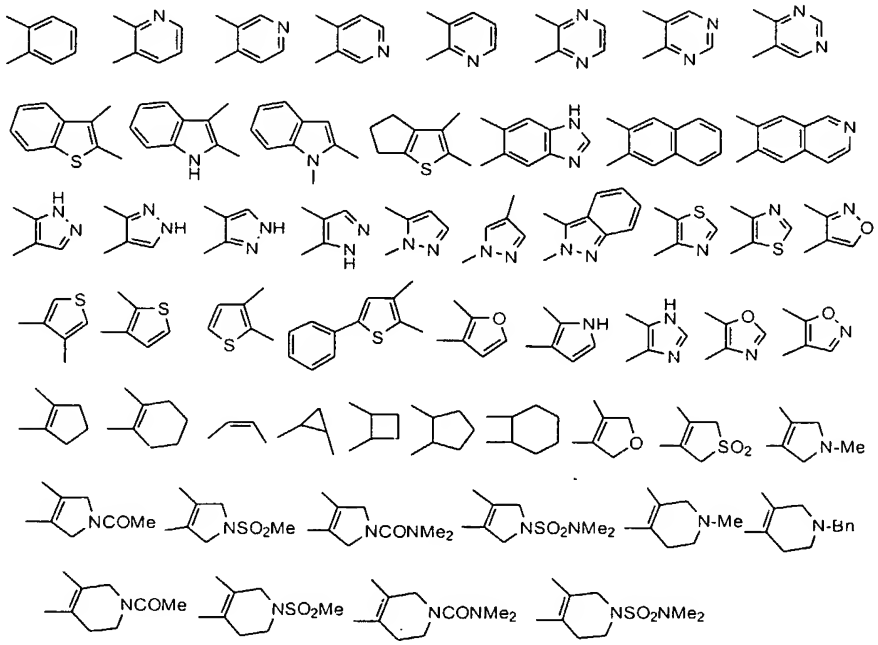
D is a direct link or is a member selected from the group consisting of:



E is a member selected from the group consisting of:

a direct link, -CH_2NH-, -$NHCH_2$-, -CH_2O-, -OCH_2-, -CH_2NH-, -CONH-, -NHCO-, -CONMe-, -NMeCO-;

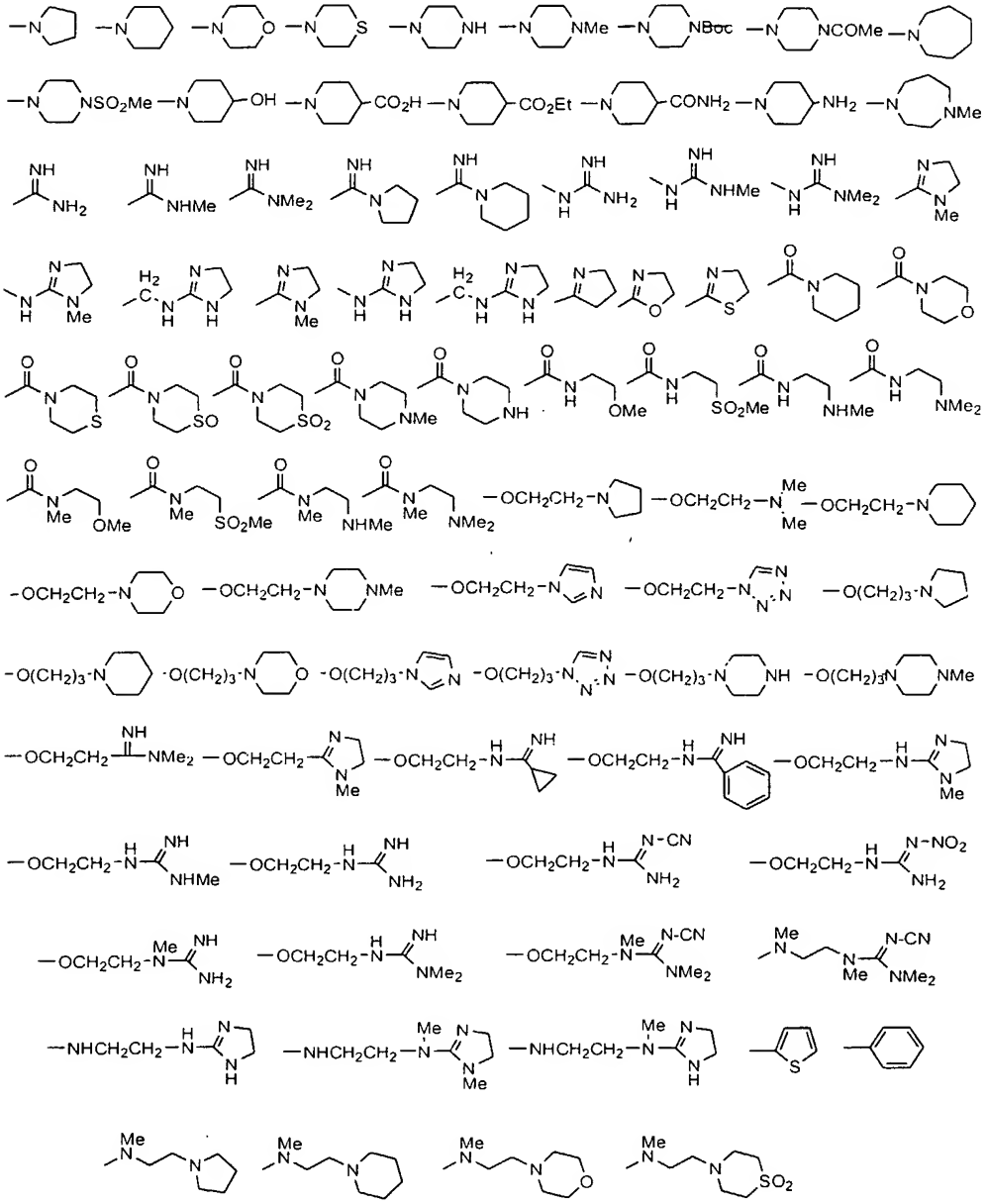
G is a member selected from the group consisting of:



G is substituted by 0-4 R^{1d} groups and each R^{1d} group is independently selected from the group consisting of:

H, -Me, -F, -Cl, -Br, aryl, heteroaryl, -NH_2, -NMe_2, -NHMe, -$NHSO_2Me$, -NHCOMe, -CH_3, -CF_3, -OH, -OCH_3, -SCH_3, -OCF_3, -OCH_2F, -$OCHF_2$, -OCH_2CF_3, -OCF_2CF_3, -NO_2, -CN, -CO_2H, -CO_2Me, -CO_2Et, -$CONH_2$, -CONHMe, -$CONMe_2$, -SO_2NH_2, -SO_2CH_3, -SO_2NMe_2, -CH_2OH, -CH_2NH_2, -CH_2NHMe, -CH_2NMe_2, -OCH_2CO_2H, -OCH_2CO_2Me, -OCH_2CO_2Et, -OCH_2CONH_2, -OCH_2CONMe_2, -$OCH_2CONHMe$, -OCH_2CH_2OMe, -OCH_2CH_2OEt, -$OCH_2CH_2NH_2$, -OCH_2CH_2NHMe, -$OCH_2CH_2NMe_2$, -$NHCH_2CH_2OMe$, -SCH_2CH_2OMe, -$SO_2CH_2CH_2OMe$, -$OCH_2CH_2SO_2Me$, -$NHCH_2CH_2NHMe$, -$NHCH_2CH_2NMe_2$, -$N(CH_2CH_2OH)_2$, -$N(CH_2CH_2OMe)_2$, -$NHCH_2CO_2H$, -$NHCH_2CO_2Et$, -$NHCH_2CO_2Et$, -$NHCH_2CONH_2$, -$NHCH_2CONMe_2$, -$NHCH_2CONHMe$, -$N(CH_3)CH_2CO_2H$,

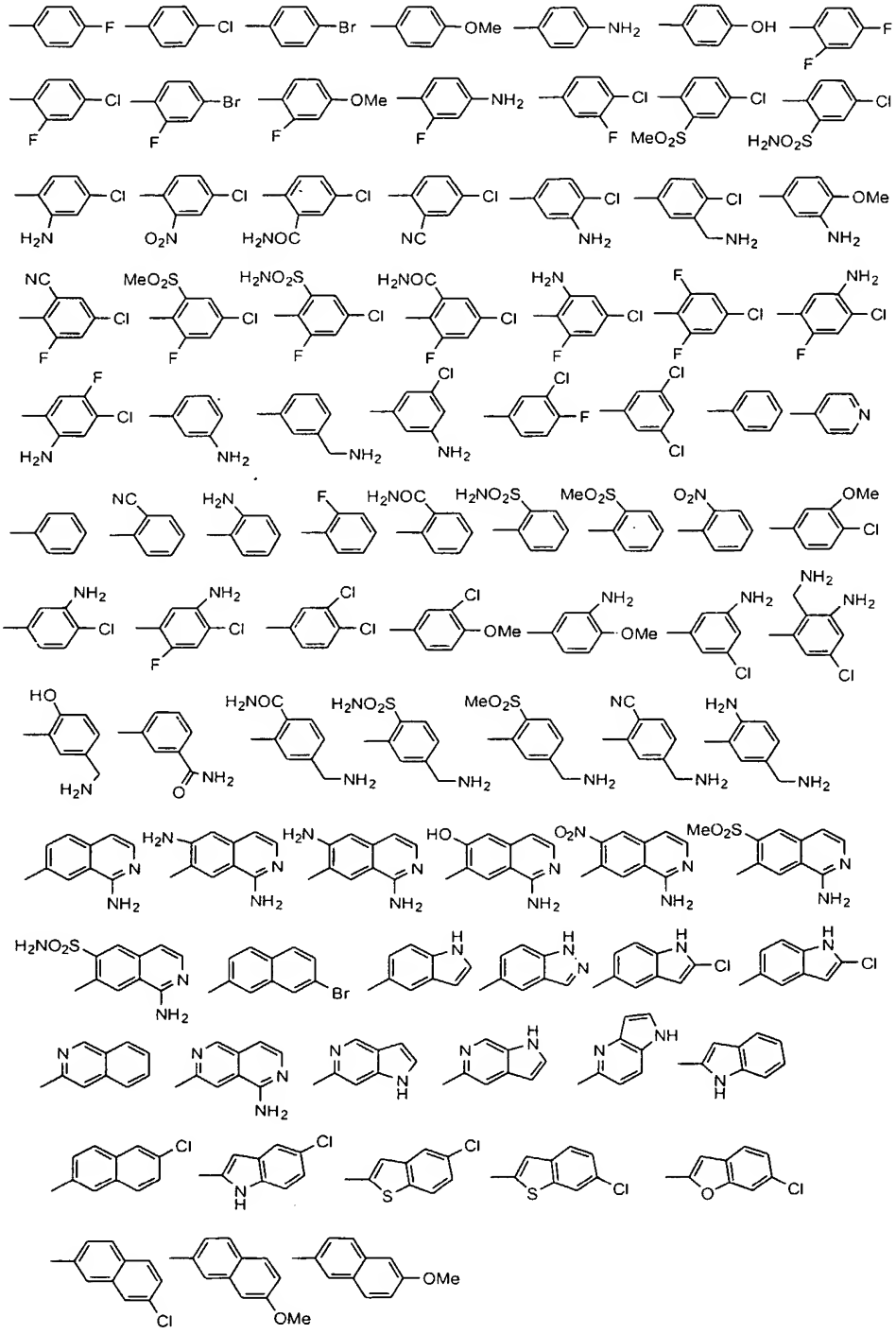
-N(CH$_3$)CH$_2$CO$_2$Et, -(NMe)CH2COOH, -N(Me)CH2CONH2, -N(Me)CH2CH2NMe2, -N(Me)CH2CH2OMe, -NHCH2CH2OMe,

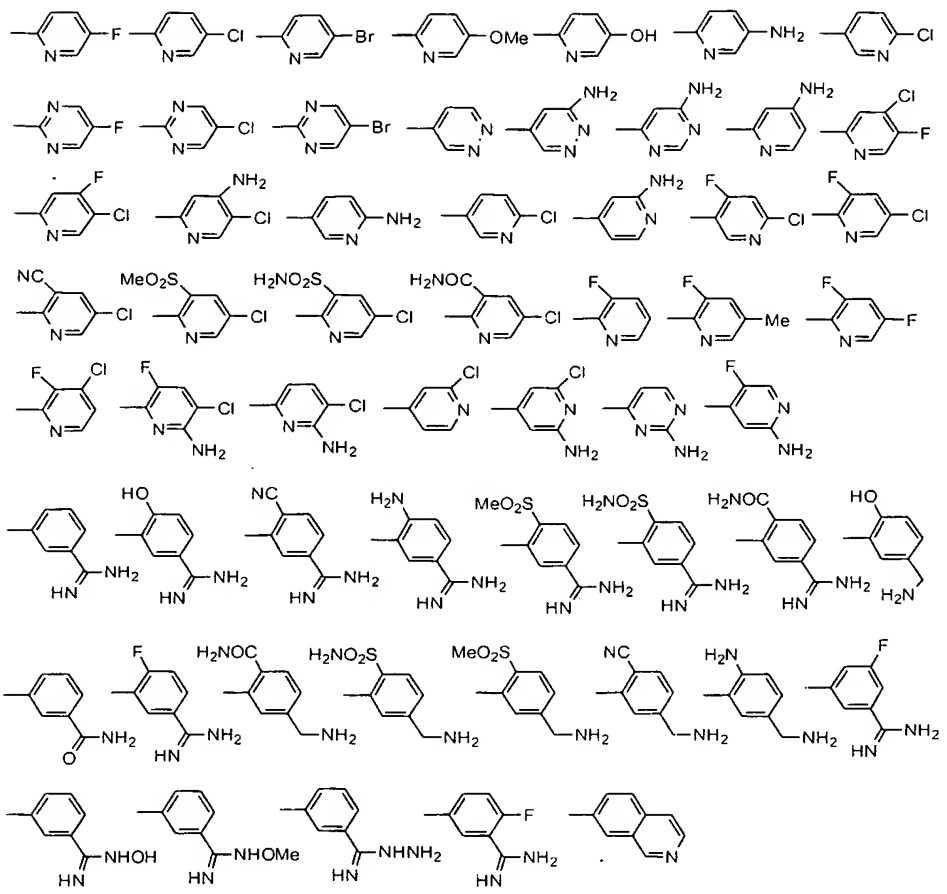


J is a member selected from the group consisting of:

a direct link, -SO2-, -CO-, -O-, -NH-, -C(=O)-NH- and -NH-C(=O)-;

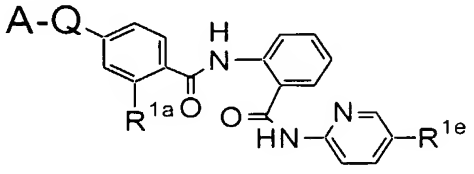
X is a member selected from the group consisting of:





and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



where:

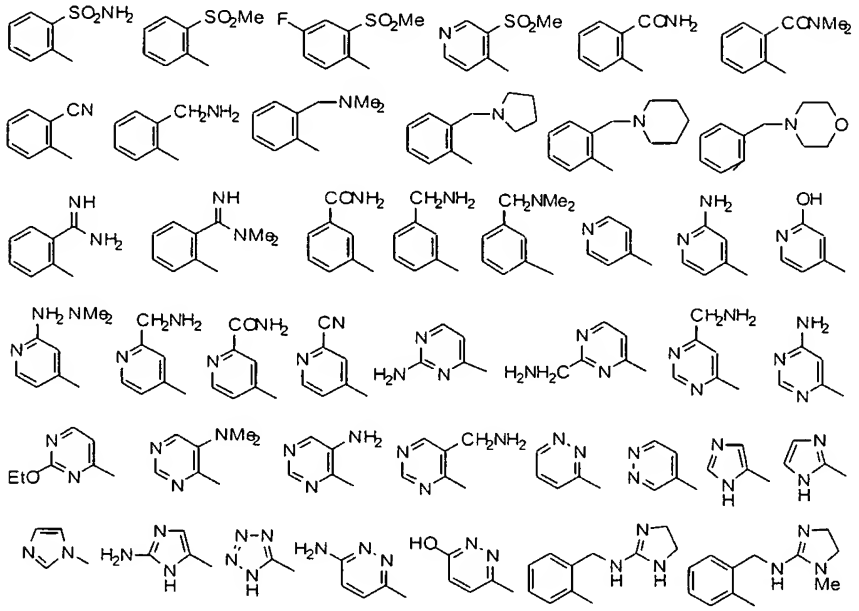
R^{1a} is a member selected from the group consisting of:

H, -F, -Cl and –Br;

R^{1e} is a member selected from the group consisting of:

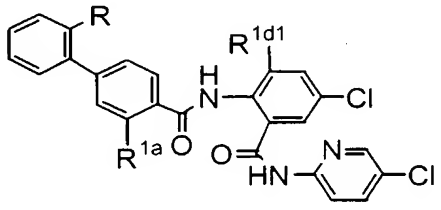
H, -F, -Cl, -Br, -OMe, -OH, -Me, $-CF_3$ and $-CH_2NH_2$; and

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, having the following structure:



wherein:

R is a member selected from the group consisting of:

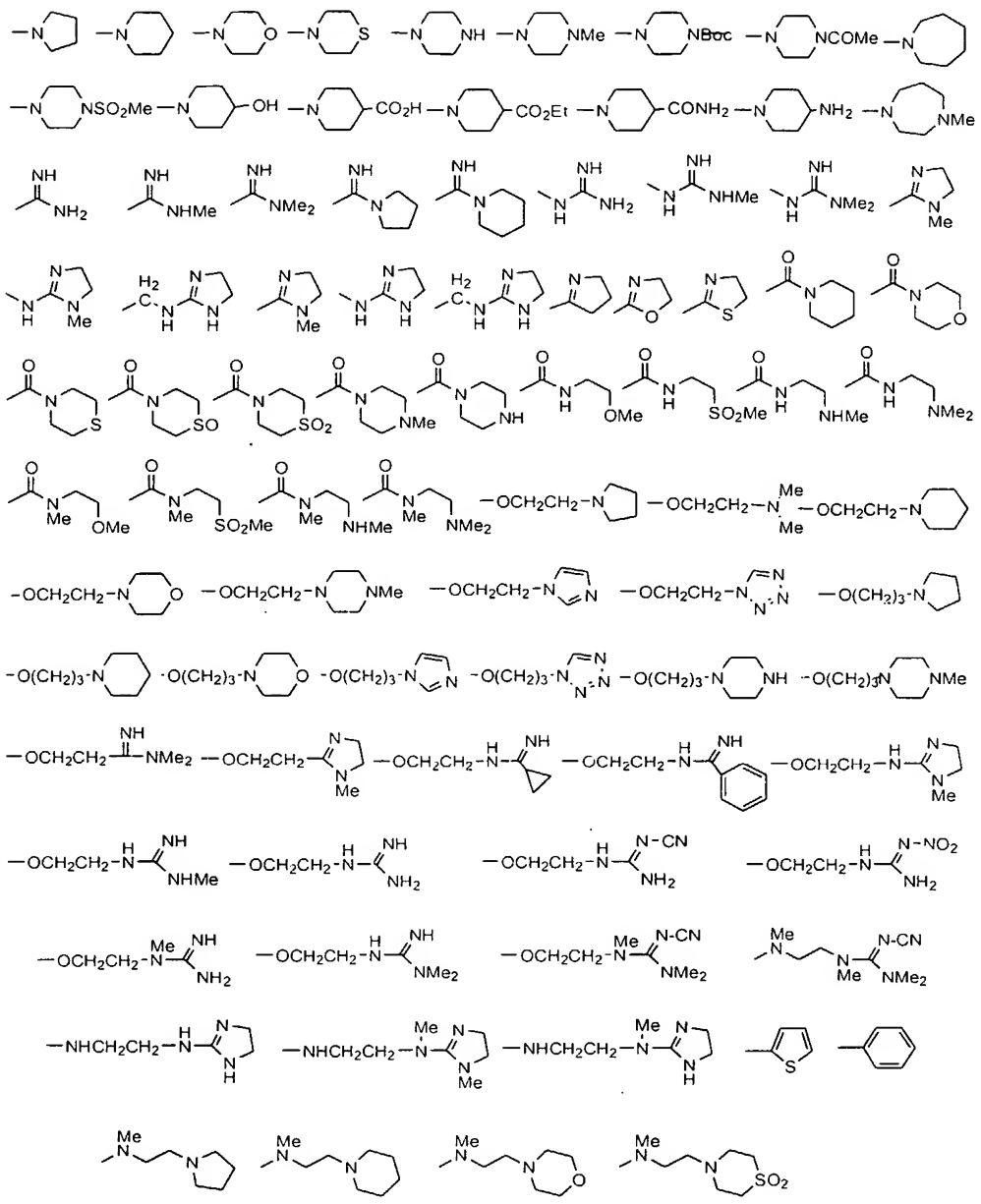
$-SO_2Me$, $-SO_2NH_2$, $-CH_2NH_2$, $-CH_2N(CH_3)_2$;

R^{1a} is a member selected from the group consisting of:

H, -F;

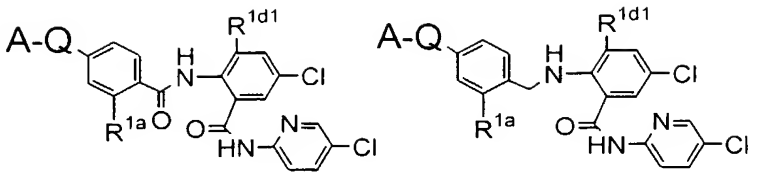
R^{1d1} is a member selected from the group consisting of:

H, -Me, -F, -Cl, -Br, aryl, heteroaryl, $-NH_2$, $-NMe_2$, -NHMe, $-NHSO_2Me$, -NHCOMe, $-CH_3$, $-CF_3$, -OH, $-OCH_3$, $-SCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CF_3$, $-NO_2$, -CN, $-CO_2H$, $-CO_2Me$, $-CO_2Et$, $-CONH_2$, -CONHMe, $-CONMe_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-SO_2NMe_2$, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHMe$, $-CH_2NMe_2$, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-OCH_2CO_2Et$, $-OCH_2CONH_2$, $-OCH_2CONMe_2$, $-OCH_2CONHMe$, $-OCH_2CH_2OMe$, $-OCH_2CH_2OEt$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-NHCH_2CH_2OMe$, $-SCH_2CH_2OMe$, $-SO_2CH_2CH_2OMe$, $-OCH_2CH_2SO_2Me$, $-NHCH_2CH_2NHMe$, $-NHCH_2CH_2NMe_2$, $-N(CH_2CH_2OH)_2$, $-N(CH_2CH_2OMe)_2$, $-NHCH_2CO_2H$, $-NHCH_2CO_2Et$, $-NHCH_2CO_2Et$, $-NHCH_2CONH_2$, $-NHCH_2CONMe_2$, $-NHCH_2CONHMe$, $-N(CH_3)CH_2CO_2H$, $-N(CH_3)CH_2CO_2Et$, -(NMe)CH2COOH, -N(Me)CH2CONH2, -N(Me)CH2CH2NMe2, -N(Me)CH2CH2OMe, -NHCH2CH2OMe,



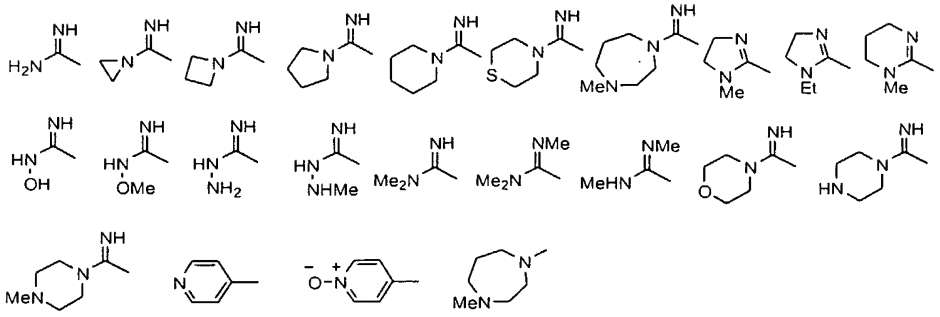
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:

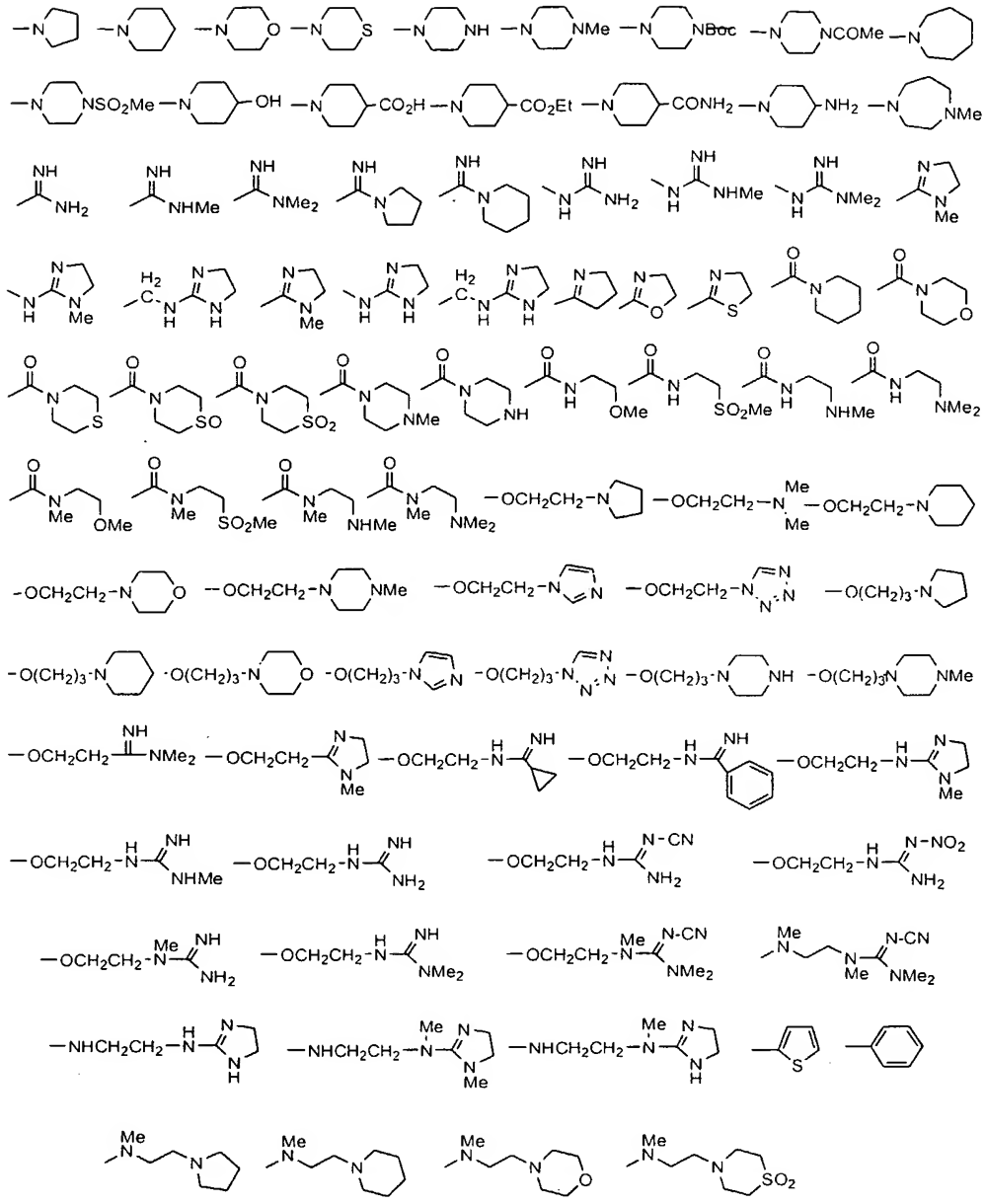


R^{1a} is a member selected from the group consisting of:

H, -F;

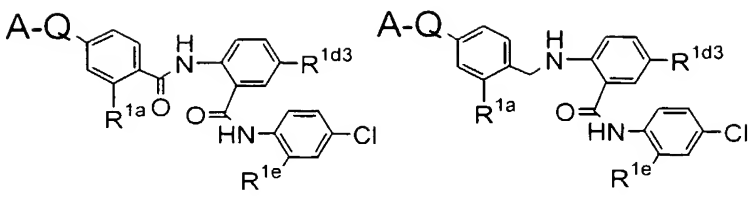
R^{1d1} is a member selected from the group consisting of:

H, -Me, -F, -Cl, -Br, aryl, heteroaryl, $-NH_2$, $-NMe_2$, -NHMe, $-NHSO_2Me$, -NHCOMe, $-CH_3$, $-CF_3$, -OH, $-OCH_3$, $-SCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CF_3$, $-NO_2$, -CN, $-CO_2H$, $-CO_2Me$, $-CO_2Et$, $-CONH_2$, -CONHMe, $-CONMe_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-SO_2NMe_2$, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHMe$, $-CH_2NMe_2$, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-OCH_2CO_2Et$, $-OCH_2CONH_2$, $-OCH_2CONMe_2$, $-OCH_2CONHMe$, $-OCH_2CH_2OMe$, $-OCH_2CH_2OEt$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-NHCH_2CH_2OMe$, $-SCH_2CH_2OMe$, $-SO_2CH_2CH_2OMe$, $-OCH_2CH_2SO_2Me$, $-NHCH_2CH_2NHMe$, $-NHCH_2CH_2NMe_2$, $-N(CH_2CH_2OH)_2$, $-N(CH_2CH_2OMe)_2$, $-NHCH_2CO_2H$, $-NHCH_2CO_2Et$, $-NHCH_2CO_2Et$, $-NHCH_2CONH_2$, $-NHCH_2CONMe_2$, $-NHCH_2CONHMe$, $-N(CH_3)CH_2CO_2H$, $-N(CH_3)CH_2CO_2Et$, -(NMe)CH2COOH, -N(Me)CH2CONH2, -N(Me)CH2CH2NMe2, -N(Me)CH2CH2OMe, -NHCH2CH2OMe,



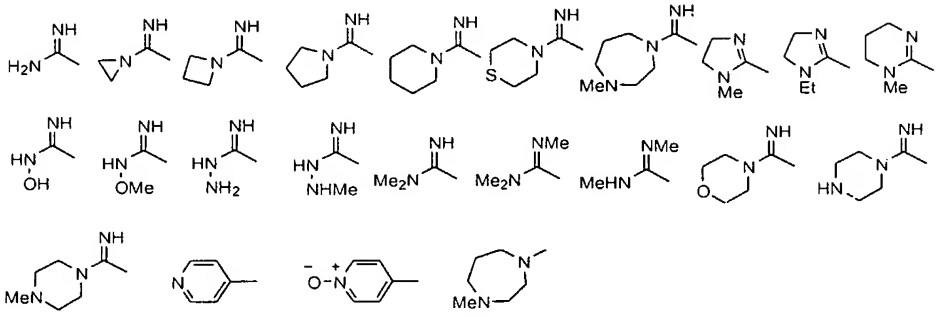
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:



R^{1a} is a member selected from the group consisting of:

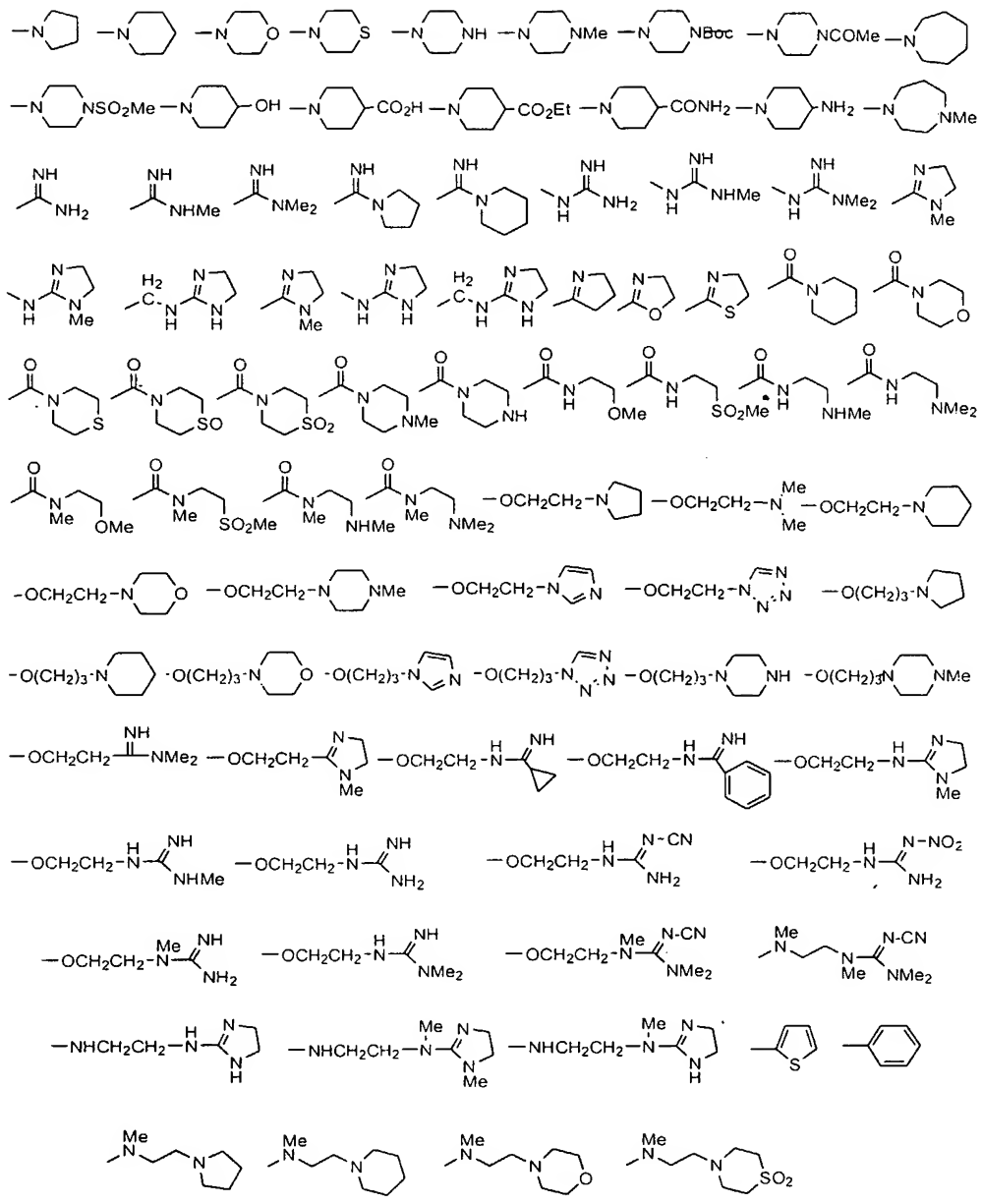
H, -F;

R^{1e} is a member selected from the group consisting of:

H, -F, $-SO_2Me$, $-SO_2NH_2$, -CN, $-CONH_2$, $-CH_2NH_2$, $-CH_2NMe_2$;

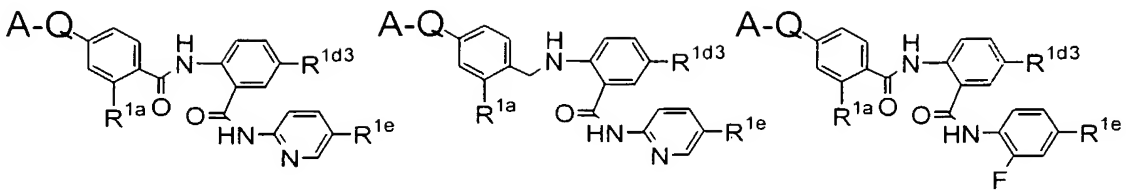
R^{1d3} is a member selected from the group consisting of:

H, -Me, -F, -Cl, -Br, aryl, heteroaryl, $-NH_2$, $-NMe_2$, -NHMe, $-NHSO_2Me$, -NHCOMe, $-CH_3$, $-CF_3$, -OH, $-OCH_3$, $-SCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CF_3$, $-NO_2$, -CN, $-CO_2H$, $-CO_2Me$, $-CO_2Et$, $-CONH_2$, -CONHMe, $-CONMe_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-SO_2NMe_2$, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHMe$, $-CH_2NMe_2$, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-OCH_2CO_2Et$, $-OCH_2CONH_2$, $-OCH_2CONMe_2$, $-OCH_2CONHMe$, $-OCH_2CH_2OMe$, $-OCH_2CH_2OEt$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-NHCH_2CH_2OMe$, $-SCH_2CH_2OMe$, $-SO_2CH_2CH_2OMe$, $-OCH_2CH_2SO_2Me$, $-NHCH_2CH_2NHMe$, $-NHCH_2CH_2NMe_2$, $-N(CH_2CH_2OH)_2$, $-N(CH_2CH_2OMe)_2$, $-NHCH_2CO_2H$, $-NHCH_2CO_2Et$, $-NHCH_2CO_2Et$, $-NHCH_2CONH_2$, $-NHCH_2CONMe_2$, $-NHCH_2CONHMe$, $-N(CH_3)CH_2CO_2H$, $-N(CH_3)CH_2CO_2Et$, -(NMe)CH2COOH, -N(Me)CH2CONH2, -N(Me)CH2CH2NMe2, -N(Me)CH2CH2OMe, -NHCH2CH2OMe,



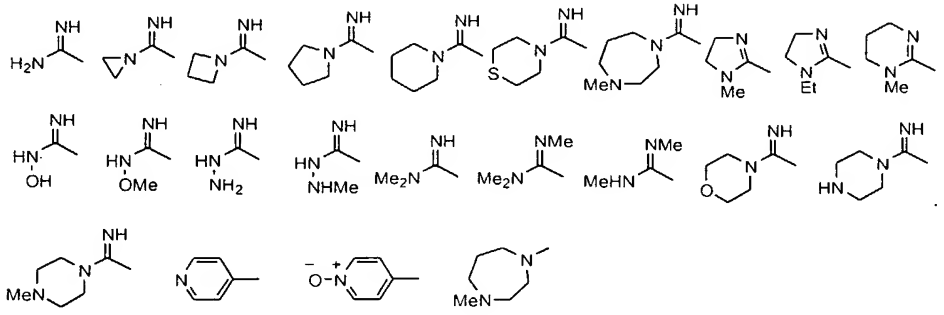
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:



R^{1a} is a member selected from the group consisting of:

H, -F;

R^{1e} is a member selected from the group consisting of:

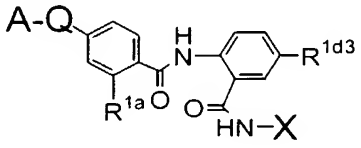
-Cl, -Br;

R^{1d3} is a member selected from the group consisting of:

H, F, Cl, Br, $-OCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CF_3$;

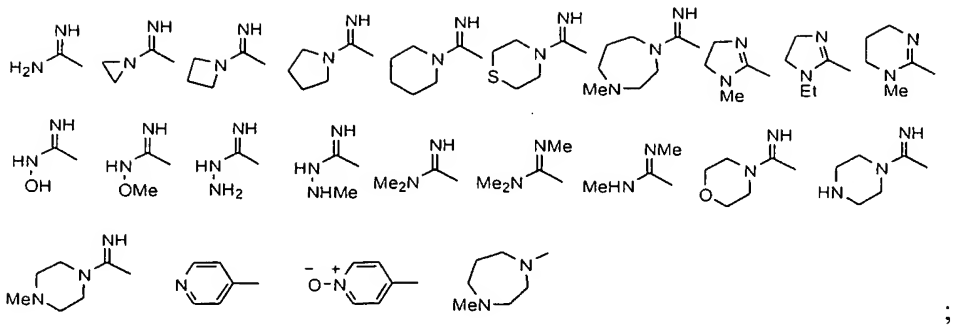
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:



;

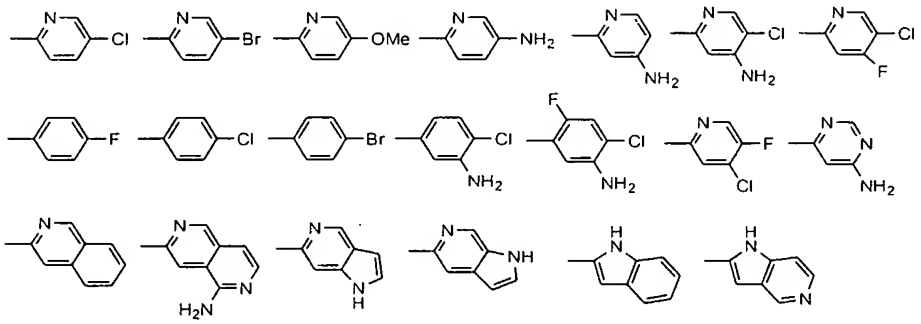
R^{1a} is a member selected from the group consisting of:

H, -F;

R^{1d3} is a member selected from the group consisting of:

H, -F, -Cl, -Br, $-OCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CF_3$, $-NHSO_2Me$, -NHAc, $-SO_2Me$, $-SO_2NH_2$;

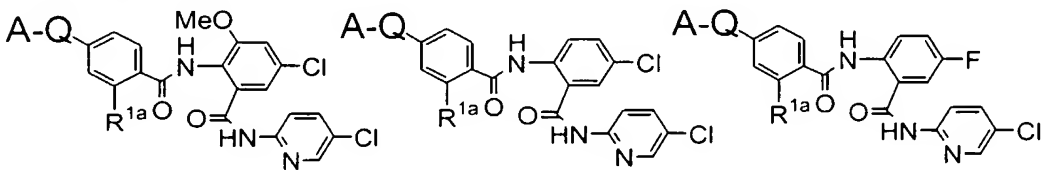
X is a member selected from the group consisting of:



;

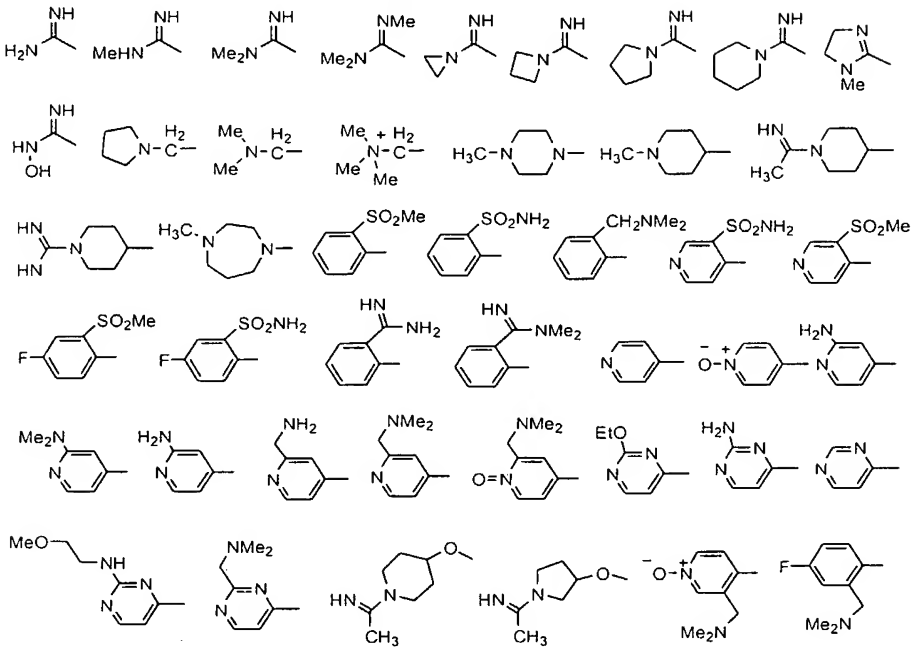
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

A-Q is a member selected from the group consisting of:



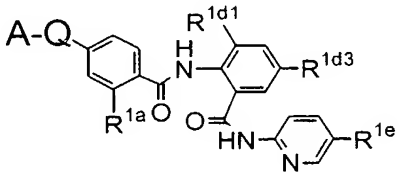
; and

R^{1a} is a member selected from the group consisting of:

H, -F;

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R^{1a} is a member selected from the group consisting of:

H, -F;

R^{1d1} is a member selected from the group consisting of:

H, -OMe;

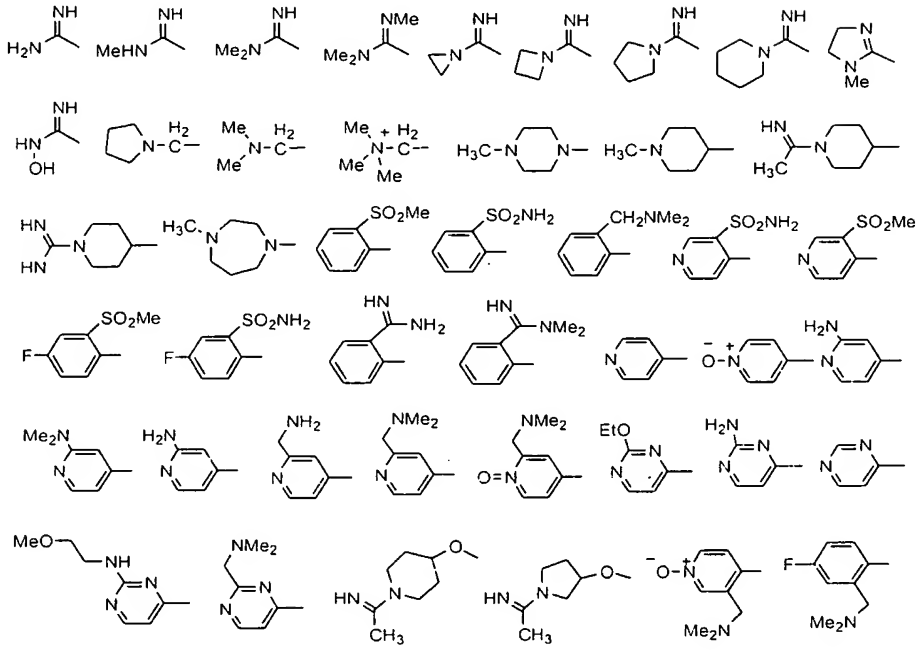
R^{1d3} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, $-OCF_3$;

R^{1e} is a member selected from the group consisting of:

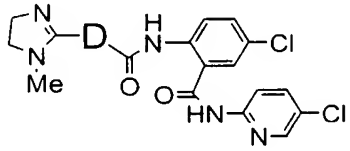
H, -F, -Cl, -Br;

A-Q is a member selected from the group consisting of:



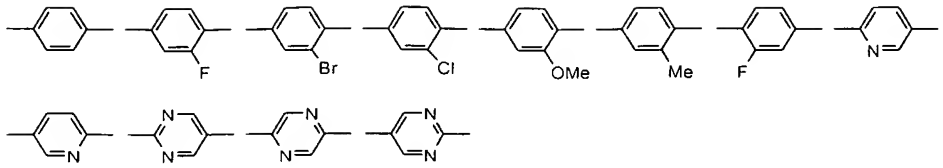
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



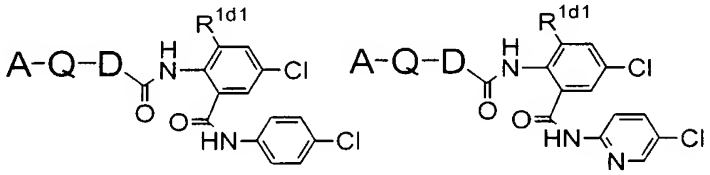
wherein:

D is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

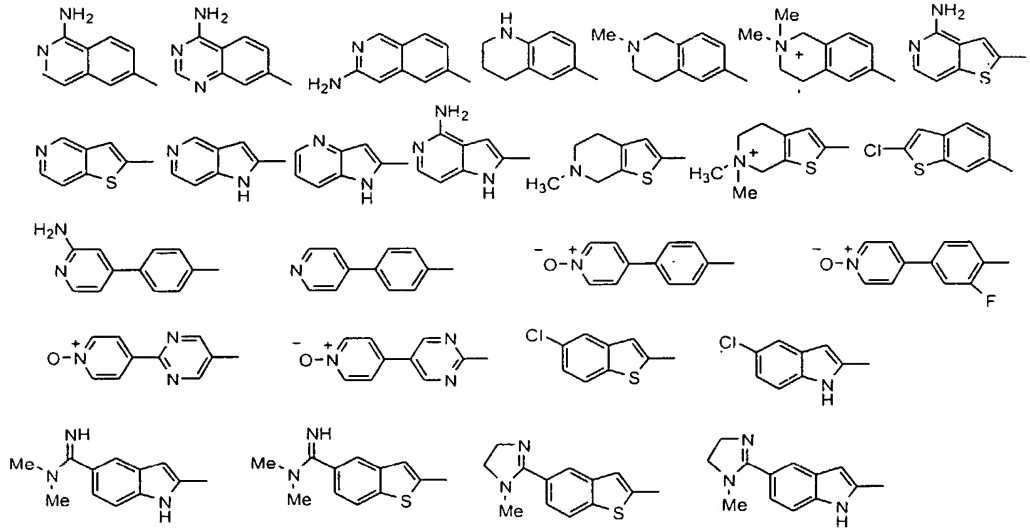
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

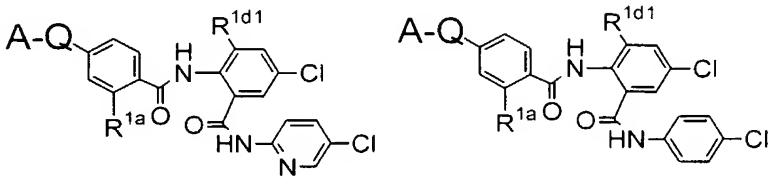
R^{1d1} is H or –OMe;

A-Q-D is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

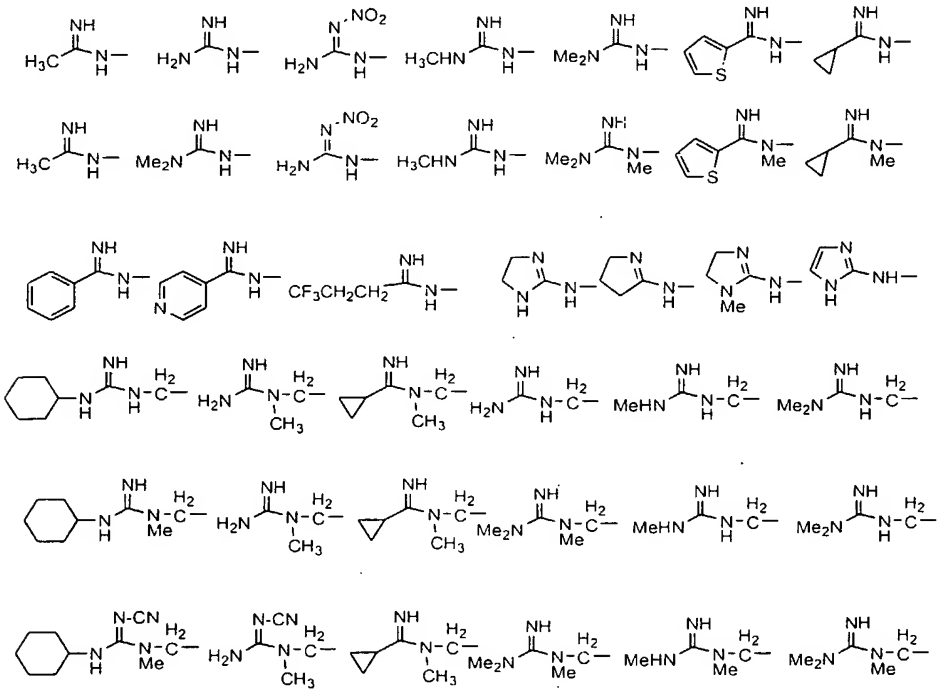


wherein:

R^{1a} is H or F;

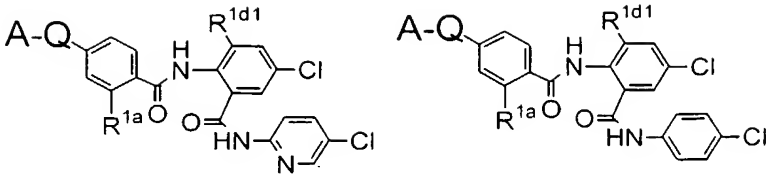
R^{1d1} is H or –OMe;

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

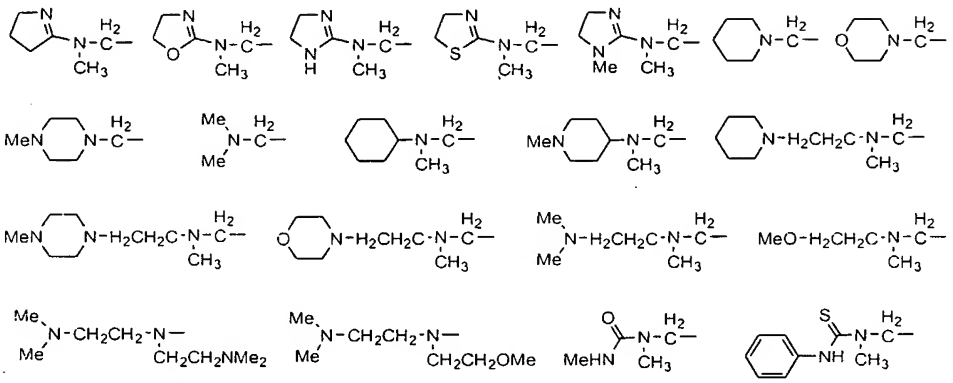


wherein:

R^{1a} is H or F;

R^{1d1} is H or –OMe;

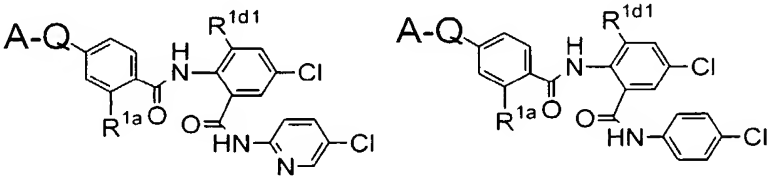
A-Q is a member selected from the group consisting of:



; and

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

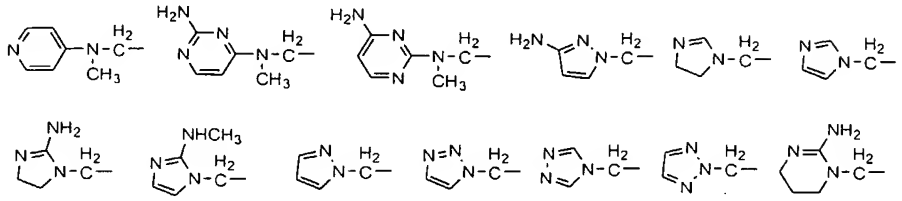


wherein:

R^{1a} is H or F;

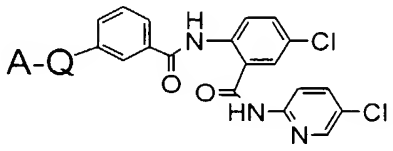
R^{1d1} is H or –OMe; and

A-Q is a member selected from the group consisting of:



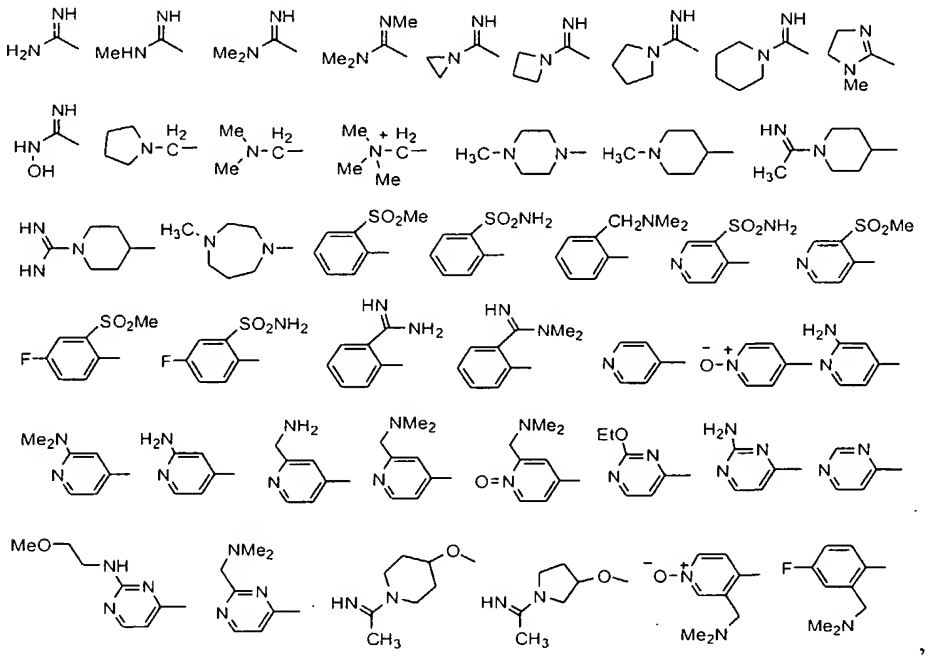
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



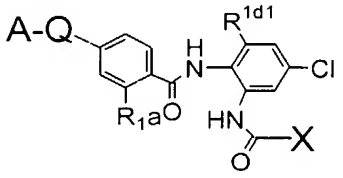
wherein:

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:

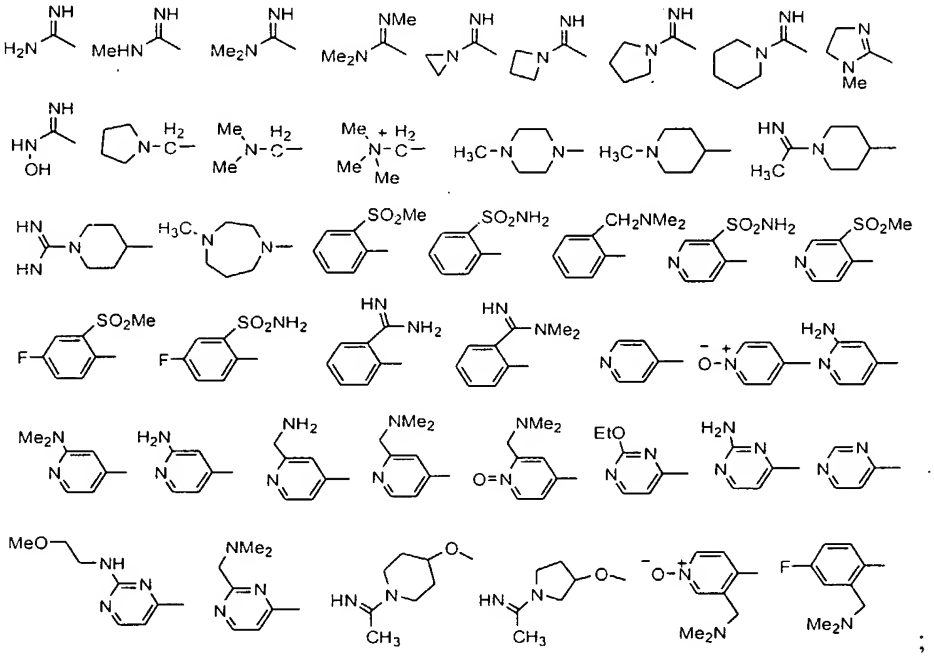


wherein:

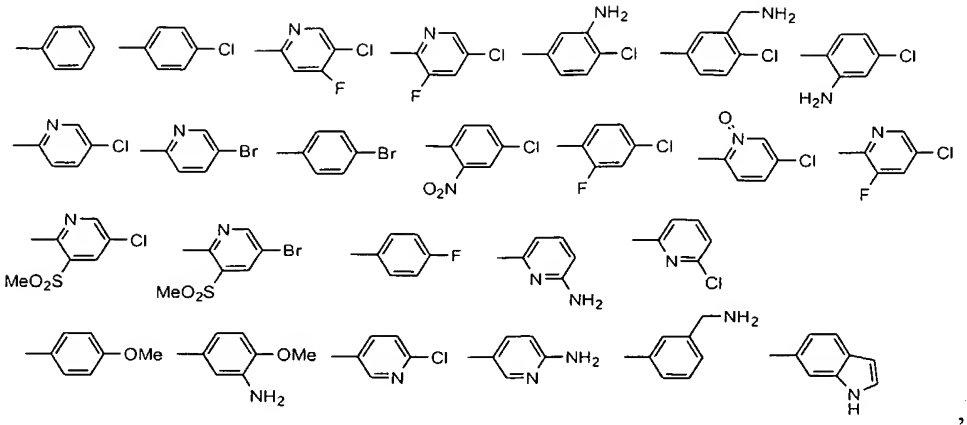
R^{1a} is H or F;

R^{1d1} is H or –OMe;

A-Q is a member selected from the group consisting of:

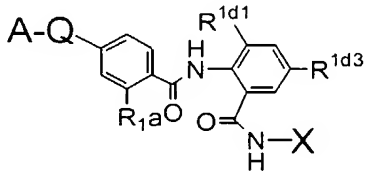


and X is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

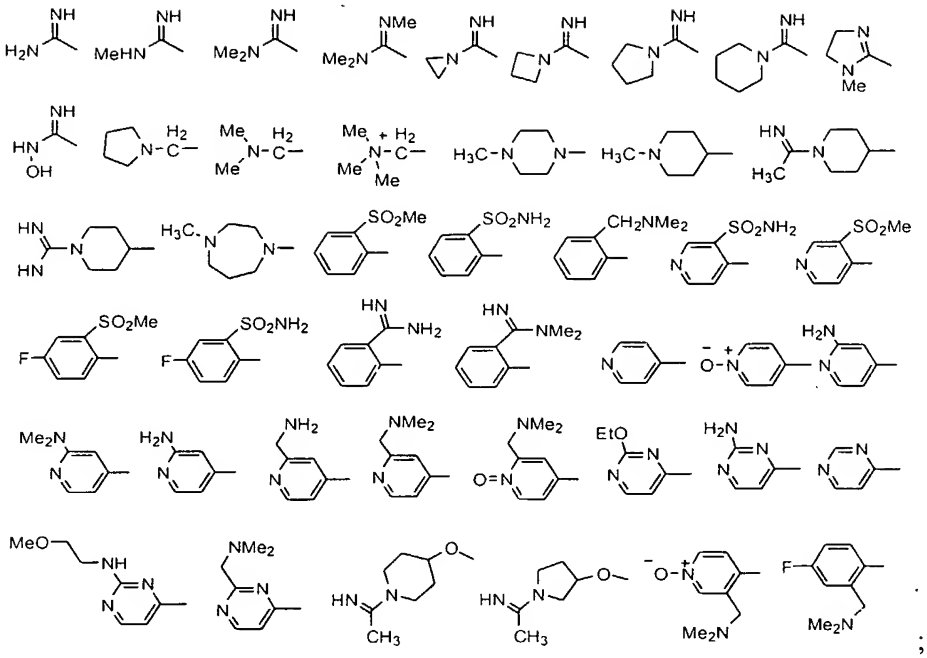
The invention provides compound of formula Ib, as describe above, having the following structure:



wherein:

R1a is H or F;

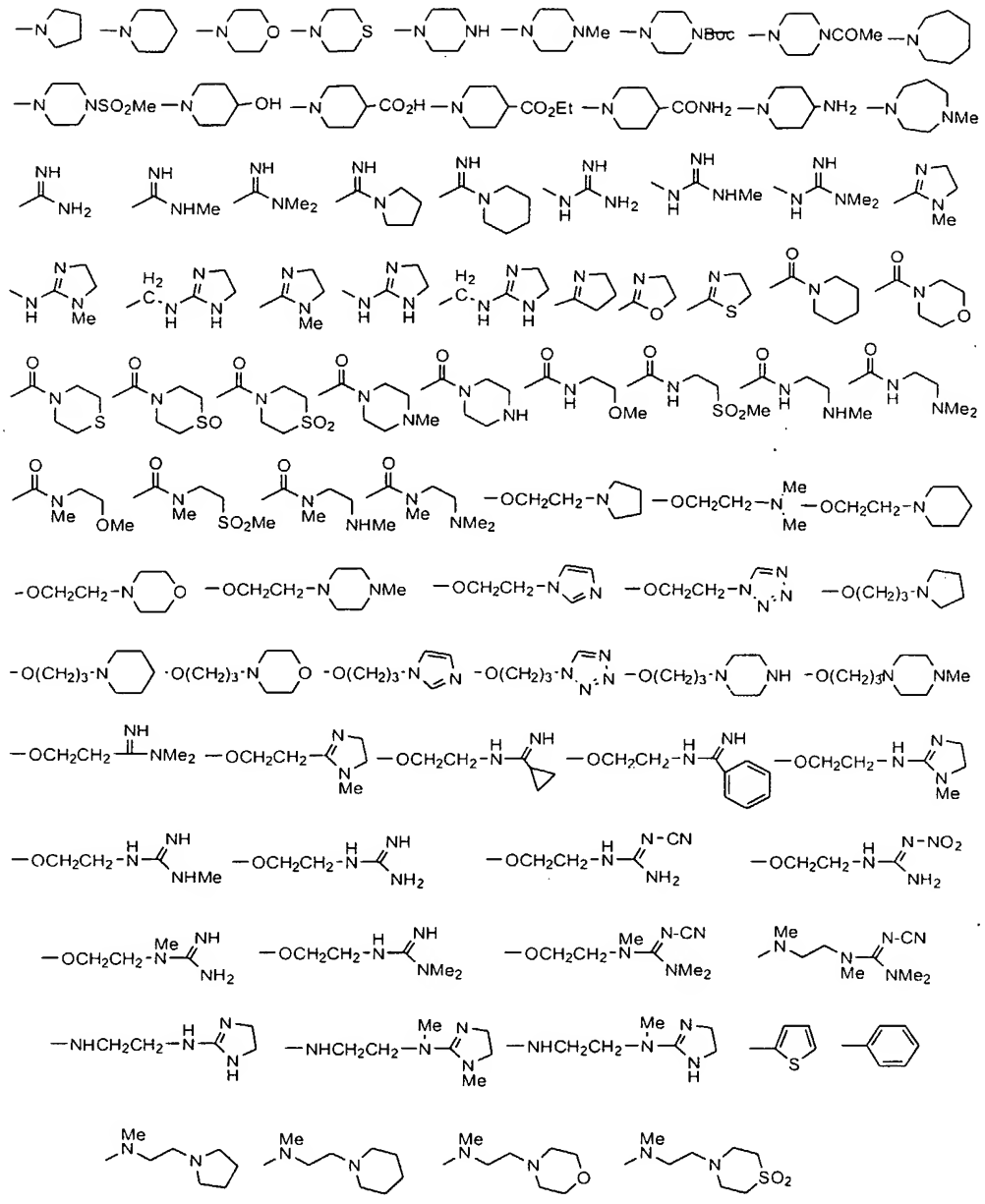
A-Q is a member selected from the group consisting of:



;

R^{1d1} is a member selected from the group consisting of:

H, -F, -Cl, -Br, aryl, heteroaryl, $-NH_2$, $-NMe_2$, -NHMe, $-NHSO_2Me$, -NHCOMe, $-CH_3$, $-CF_3$, -OH, $-OCH_3$, $-SCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CF_3$, $-NO_2$, -CN, $-CO_2H$, $-CO_2Me$, $-CO_2Et$, $-CONH_2$, -CONHMe, $-CONMe_2$, $-SO_2NH_2$, $-SO_2CH_3$, $-SO_2NMe_2$, $-CH_2OH$, $-CH_2NH_2$, $-CH_2NHMe$, $-CH_2NMe_2$, $-OCH_2CO_2H$, $-OCH_2CO_2Me$, $-OCH_2CO_2Et$, $-OCH_2CONH_2$, $-OCH_2CONMe_2$, $-OCH_2CONHMe$, $-OCH_2CH_2OMe$, $-OCH_2CH_2OEt$, $-OCH_2CH_2NH_2$, $-OCH_2CH_2NHMe$, $-OCH_2CH_2NMe_2$, $-NHCH_2CH_2OMe$, $-SCH_2CH_2OMe$, $-SO_2CH_2CH_2OMe$, $-OCH_2CH_2SO_2Me$, $-NHCH_2CH_2NHMe$, $-NHCH_2CH_2NMe_2$, $-N(CH_2CH_2OH)_2$, $-N(CH_2CH_2OMe)_2$, $-NHCH_2CO_2H$, $-NHCH_2CO_2Et$, $-NHCH_2CO_2Et$, $-NHCH_2CONH_2$, $-NHCH_2CONMe_2$, $-NHCH_2CONHMe$, $-N(CH_3)CH_2CO_2H$, $-N(CH_3)CH_2CO_2Et$, -(NMe)CH2COOH, -N(Me)CH2CONH2, -N(Me)CH2CH2NMe2, -N(Me)CH2CH2OMe, -NHCH2CH2OMe,

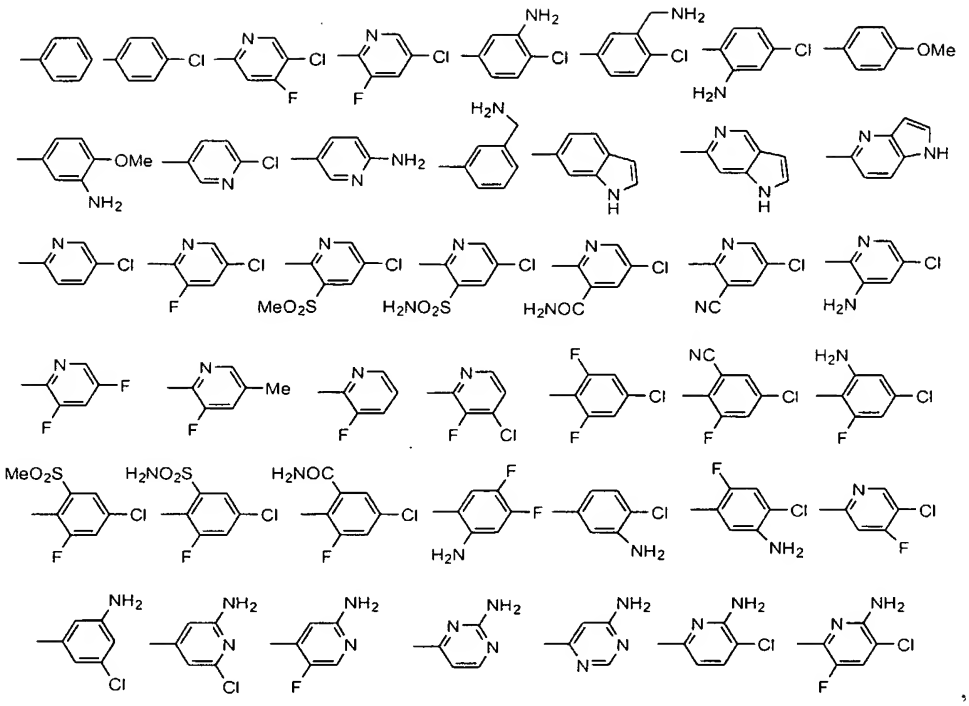


;

R^{1d3} is a member selected from the group consisting of:

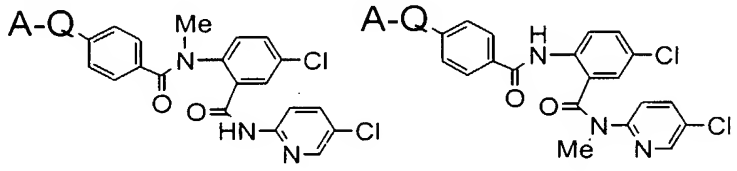
H, -F, -Cl, -Br, $-OCH_3$, $-OCF_3$, $-OCH_2F$, $-OCHF_2$, $-OCH_2CF_3$, $-OCF_2CF_3$; and

X is a member selected from the group consisting of:



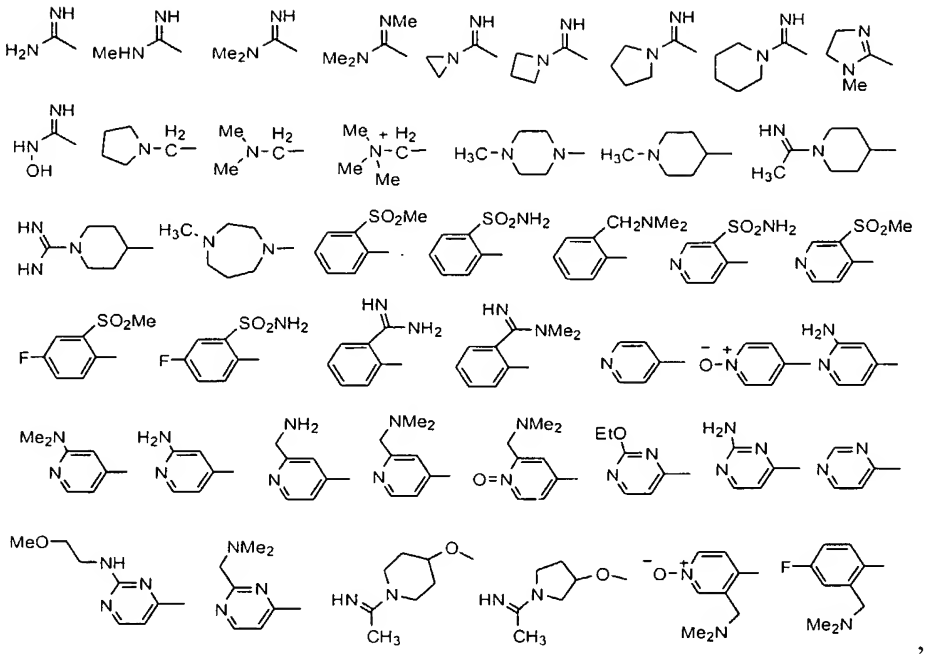
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



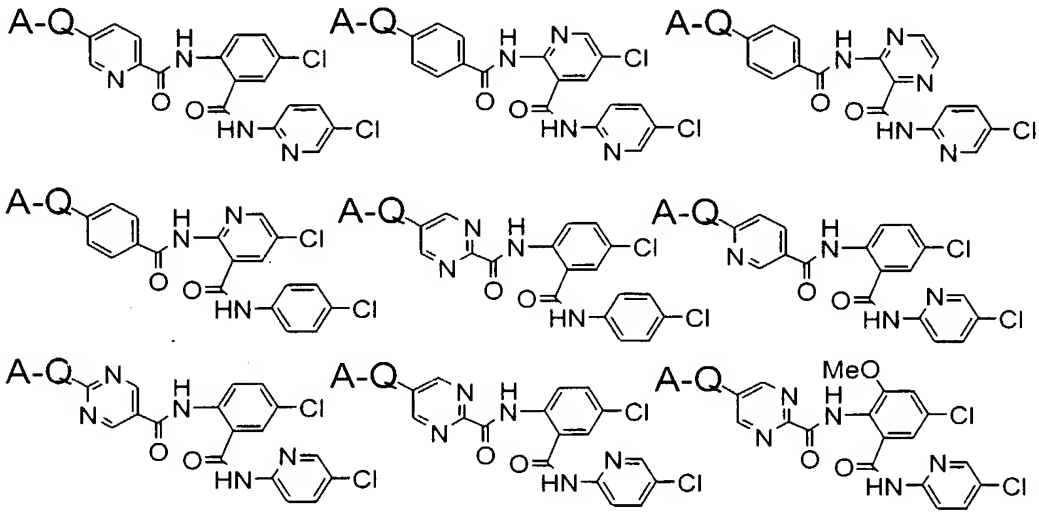
wherein:

A-Q is a member selected from the group consisting of:



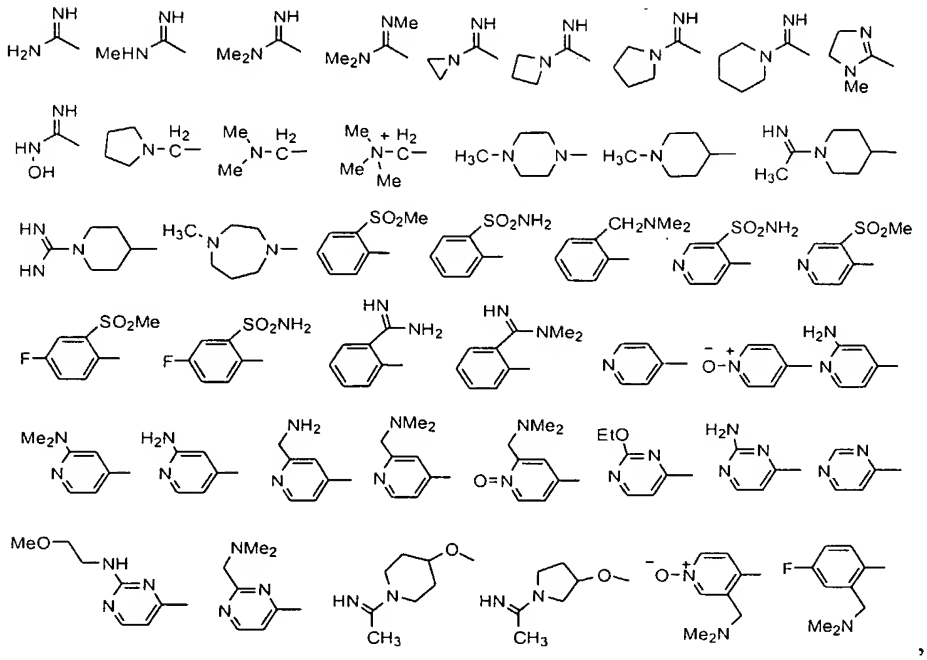
and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

The invention provides compound of formula Ib, as described above, having the following structure:



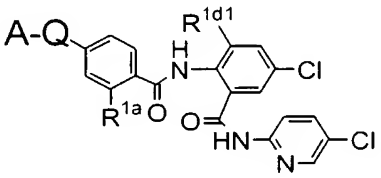
wherein:

A-Q is a member selected from the group consisting of:



and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

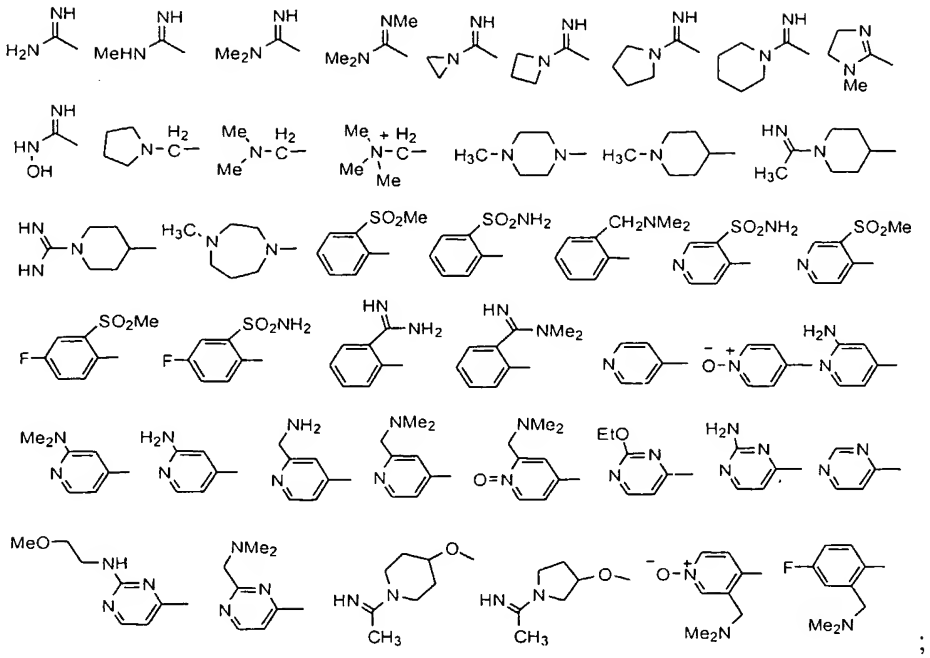
The invention provides compound of formula Ib, as described above, having the following structure:



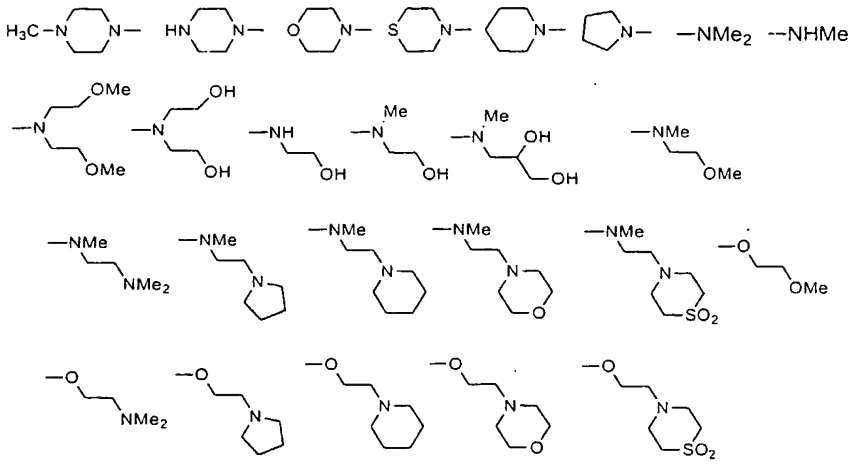
wherein:

R^{1a} is H or F;

A-Q is a member selected from the group consisting of:



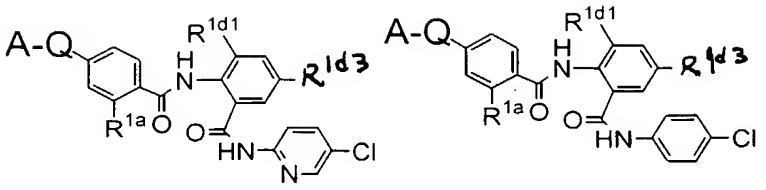
R^{1d1} is a member selected from the group consisting of: H, OMe, Cl, F, OCF_3,



-N(Me)COOEt, -N(Me)CH2OOH,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

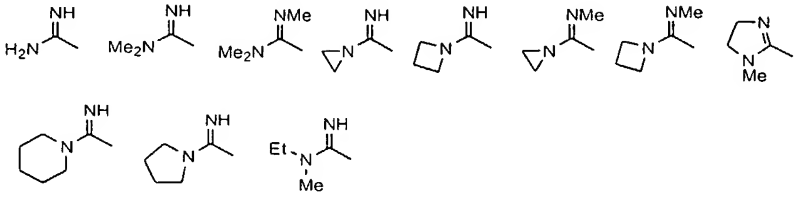
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R1a is H or F;

A-Q is a member selected from the group consisting of:



;

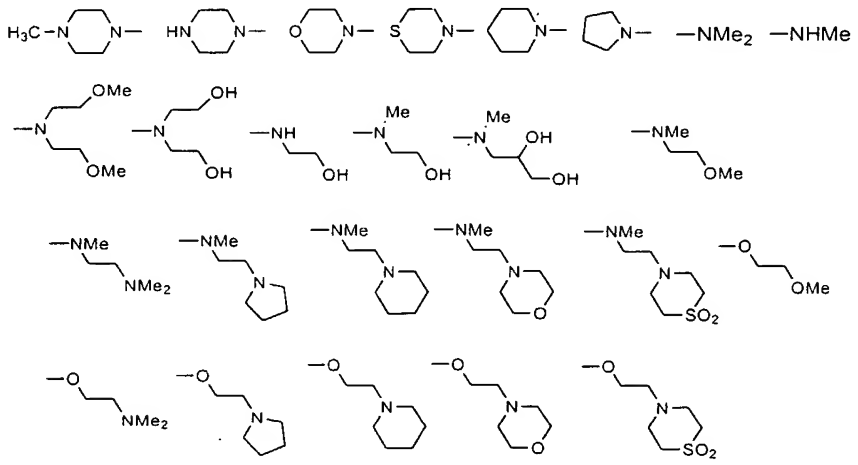
R^{1d1} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, $-OCF_3$, -OH, $-NMe_2$, $-OCH_2CO_2Et$, $-OCH_2CO_2H$;

R^{1d3} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, $-OCF_3$, -OH, $-NMe_2$, $-OCH_2CO_2Et$, $-OCH_2CO_2H$,

$-OCF_2H$, $-OCFH_2$, $-OCF_2CF_3$, $-OCH_2CH_3$,

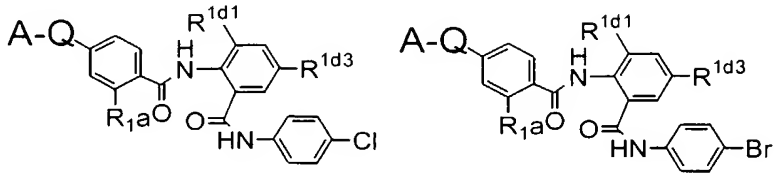


-N(Me)COOEt, -N(Me)CH2OOH

,

and all pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives thereof.

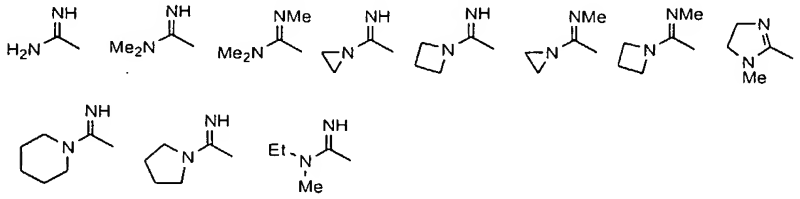
The invention provides compound of formula Ib, as described above, having the following structure:



wherein:

R1a is H or F;

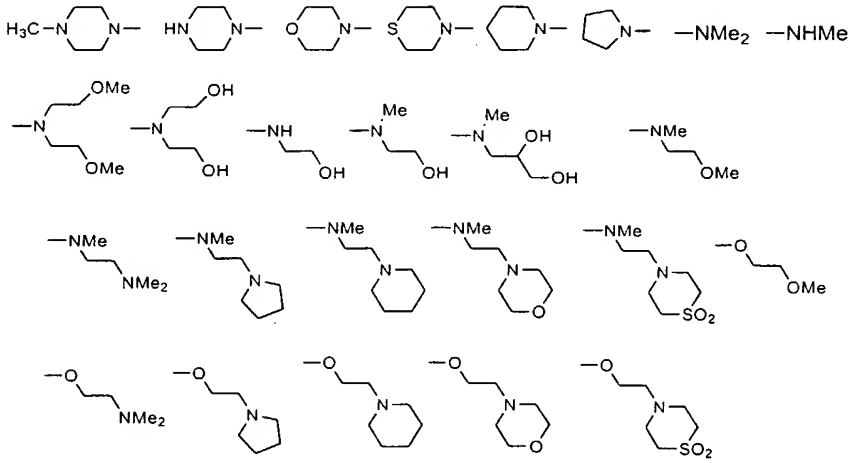
A-Q is a member selected from the group consisting of:



;

R^{1d1} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, $-OCF_3$, -OH, $-NMe_2$, $-OCH_2CO_2Et$, $-OCH_2CO_2H$



-N(Me)COOEt, -N(Me)CH2OOH ;

R^{1d3} is a member selected from the group consisting of:

H, -F, -Cl, -Br, -OMe, $-OCF_3$, -OH, $-NMe_2$, $-OCH_2CO_2Et$, $-OCH_2CO_2H$, $-OCF_2H$, $-OCFH_2$, $-OCF_2CF_3$, $-OCH_2CH_3$.